It has been reported that sertraline moderately inhibits cyp2D6 (Greenblatt *et al.*, 1998) and its inhibitory effects of cyp 2D6 and other cyp isoenzymes are dose-related fashion (Spina *et al.*, 2004). The major enzyme of risperidone to 9-hydroxyrisperidone is cyp2D6, and to some extent cyp3A4 (Fang *et al.*, 1999). Taking these findings into account, it is plausible to assume that sertraline increases plasma risperidone levels, which leads to the emergence of extrapyramidal symptoms. Actually, we have previously demonstrated a positive correlation was found between plasma levels of risperidone and 9-hydrtoxyrisperidone and the emergence of extrapyramidal symptoms in Japanese populations (Yoshimura *et al.*, 2001). In the present study, coadministration of sertraline with risperidone did not deteriorate extrapyramidal symptoms, because the dose of risperidone was small, and the plasma levels of active moiety of risperidone was low level. Otherwise, larger dosage of sertraline might be needed to increase plasma levels of active moiety of risperidone. Since sertraline itself has been reported to cause extrapyramidal symptoms (Lambert *et al.*, 1998), clinicians should be aware of the possibility of extrapyramidal symptoms developing when sertraline and risperidone are coadministered.

We have recently reported that serum BDNF levels in patients with responders to paroxetine or milnacipran were raised at 8 weeks after their treatment, while those in nonresponders were not. These results suggest that serum BDNF levels can be considered state markers in depression. In the present study, a significant increase was found in serum BDNF levels after risperidone addition in responders, while these levels were not altered in nonresponders. Basically, the present results regarding serum BDNF levels are in accordance with those of our previous study (Yoshimura *et al.*, 2007). Interestingly, serum BDNF levels in responders to risperidone addition were raised at 4 weeks, but not 8 weeks after risperidone addition, suggesting that the effects of risperidone combined with sertraline on serum BDNF levels might be more potent than those of each drug. The source of circulating BDNF remains unknown. Platelet, brain neurons, and vascular endothelial cells are currently considered to be putative sources. It has been demonstrated that BDNF crosses the blood–brain barrier (Pan *et al.*, 1998) and that BDNF levels in the brain and serum have been shown to undergo similar changes during the maturation and aging process in rats (Karege *et al.*, 2002). These results indicate that blood BDNF levels might in part reflect the BDNF levels in the brain. Nonetheless, it remains unclear to what extent peripheral levels reflect brain BDNF levels.

In conclusion, the addition of risperidone to sertraline is effective and well tolerated for sertraline-resistant refractory depressive patients. Addition of risperidone to sertraline does not seem to influence sertraline metabolism. In addition, the serum BDNF levels were increased in responders to risperidone, while these levels were not altered in nonresponders. The limitations of this study, including the small number of patients and the open setting should be considered. Therefore, further studies must be performed to confirm our preliminary findings.

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Progress in Neuro-Psychopharmacology & Biological Psychiatry 32 (2008) 1185–1190

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Efficacy of electroconvulsive therapy is associated with changing blood levels of homovanillic acid and brain-derived neurotrophic factor (BDNF) in refractory depressed patients: A pilot study

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ARTICLE INFO

Article history:
Received 28 November 2007
Received in revised form 21 February 2008
Accepted 21 February 2008
Available online 29 February 2008

Keywords:
Electroconvulsive therapy
Homovanillic acid
3-methoxy-4-hydroxyphenylglycol
Brain-derived neurotrophic factor
Nitric oxide
Refractory depression

ABSTRACT

Electroconvulsive therapy (ECT) is effective for patients with antidepressant medication-resistant depression. However, the mechanisms of ECT's effectiveness for treating depression are not fully understood. We therefore investigated ECT's effects on blood levels of brain-derived neurotrophic factor (BDNF), catecholamine metabolites, and nitric oxide (NO) in 18 treatment-refractory depressed patients. Serum BDNF levels increased significantly following ECT in responders to ECT (before ECT: 8.0±9.7 ng/mL; five weeks after start of ECT: 15.1±11.1 ng/mL), whereas BDNF levels in non-responders were unchanged (before ECT: 11.5±11.0 ng/mL; five weeks after start of ECT: 9.4±7.5 ng/mL). Furthermore, the plasma HVA levels, but not MHPG levels, were significantly reduced after ECT (before ECT: 8.5±1.9 ng/mL; five weeks after start of ECT: 5.8±2.2 ng/mL). This latter finding occurred in parallel with the improvement of depressive symptoms in all patients. These results suggest that the mechanisms underlying ECT's effect on refractory depression may be related to dopaminergic neurons and BDNF.

1. Introduction

Depression, like anxiety disorder, is one of the most common psychiatric disorders, with a lifetime prevalence estimated to be between 1.5% and 19% (Weissman et al., 1996). Approximately half of the depressed patients experience a chronic course and up to 20% of that half show insufficient responses to antidepressant medication (Hussain and Cochrane, 2004). In other words, despite the administration of several different antidepressants, a considerable number of depressive patients do not adequately respond to the antidepressant therapy or others do not tolerate the side effects of antidepressants. Unlike antidepressant treatment, electroconvulsive therapy (ECT) has a shorter onset latency and has been used for patients with serious or treatment-refractory depression (Burt et al., 2002). ECT is one of the eligible strategies for treatment-refractory depression (UK ECT Review Group, 2003).

Brain-derived neurotrophic factor (BDNF), a major neurotrophic factor, has been found to play a critical role in long-term potentiation, a cellular mechanism of learning and memory, suggesting that it can influence neuroplasticity (Figurov et al., 2006). BDNF is also needed for the survival and guidance of neurons during development as well as the survival and function of neurons during adulthood (Duman et al., 2000). There is growing evidence that BDNF may have a crucial role in mental disorders such as depression (Durman et al., 1997; Dwivedi et al., 2003) and schizophrenia (Shoval and Weizman, 2005). Karege et al. (2000a) have 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 differ from control levels. Aydemir et al. (2005) reported that serum BDNF levels are lower in depressed patients than in controls, and that treatment with antidepressant drugs for 12 weeks increases serum BDNF to control levels. Gonul et al. (2005) also reported that eight weeks of treatment with each of several antidepressant drugs significantly increases serum BDNF to control levels. These results indicate that antidepressant drugs increase serum BDNF levels in depressed patients.

Preclinical studies have demonstrated that ECT produces a robust increase in BDNF mRNA (Durman et al., 1997; Nibuya et al., 1995) and BDNF protein (Altar et al., 2004) in different rat brain areas. Some reports have demonstrated that ECT increases serum or plasma levels of BDNF (Marano et al., 2007). In contrast, another report has shown that ECT does not increase serum BDNF levels (Gronli et al., 2007). Because of these conflicting results, it remains to open question as to whether or not ECT could affect the peripheral levels of BDNF in depressed patients.

ECT does not appear to cause consistent changes in cerebrospinal fluid (CSF), plasma, or urinary levels of the major monoamine metabolites.

Abbreviations: ECT, electroconvulsive therapy; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; BDNF, brain-derived neurotrophic factor; NO, nitric oxide.

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0278-5846/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.pnpbp.2008.02.009

Some studies have reported either an increase or no change after ECT in homovanillic acid (HVA), a major metabolite of dopamine, 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of noradrenaline, or 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of serotonin (Jori et al., 1975; Abrams et al., 1976; Linnoila et al., 1984; Aberg-Wistedt et al., 1986; Devanand et al., 1989; Lykouras et al., 1990). Alternatively, others have reported reduced CSF levels of HVA, MHPG, and 5-HIAA following ECT (Harnryd et al., 1979; Lerer and Belmarker, 1982). Interestingly, crosstalk between BDNF synthesis and monoaminergic systems has been reported (Alter et al., 1992; Juric et al., 2006; Do et al., 2007; Paredes et al., 2007). For example, Paredes et al. (2007) found that BDNF evoked dopamine release in a dose dependent fashion in the rat hippocampus. Juric et al. (2006) also reported that BDNF increased dopamine synthesis in cultured neonatal rat astrocytes. Finally, Do et al. (2007) reported that BDNF upregulated the expression of D1 receptor in catecholaminergic cell lines. Recently, we also reported a negative correlation between serum BDNF levels and plasma MHPG levels in healthy hospital workers, suggesting that excessive noradrenaline might suppress BDNF synthesis and/or secretion (Mitoma et al., 2008).

It has been reported that nitric oxide (NO) is associated with the pathogenesis of depression. Plasma metabolites of NO (NOx) are lower in patients with depression, and treatment with antidepressants changes plasma NOx levels (Chrapko et al., 2004, 2006). Therefore, it is possible that ECT will also affect plasma NOx levels. Taken together, these findings suggest it is plausible that BDNF, catecholamines, and NO might play important roles in the pathogenesis of depression, and ECT should influence these factors (Linnoila et al., 1983; Rosen et al., 2003).

In the present study, we hypothesized that ECT could alter blood levels of BDNF, catecholamines, and NO, and that these alterations are associated with its clinical efficacy. To test this hypothesis, we investigated ECT's effects on serum BDNF levels, plasma levels of catecholamine metabolites, and NOx in patients with antidepressant-refractory depression.

1.1. Subjects and methods

This study included 18 inpatients (nine male, nine female) at our university hospital who met the DSM-IV-TR criteria for major depressive disorder or bipolar I disorder (depressive episode) and patients who scored at least a 15 on the 17-item version of the Hamilton Rating Scale for Depression (Ham-D). Five of the 18 patients had exhibited psychotic symptoms. The age of the subjects ranged from 31 to 78 years (mean ± SD = 60.6 ± 14.1). All patients were physically healthy and had no history of alcohol or drug abuse or co-morbid anxiety or personality disorders. The mean Mini Mental State examination was 27.8 ± 2.1. For each patient, an independent psychiatrist recommended ECT according to his or her clinical judgment based on the patient's drug resistance. Drug resistance was defined as a failure to respond to at least three courses of a single antidepressant medication with adequate dose and duration (stage III definition from Thase and Rush, 1997).

A medical history and a physical examination together with blood and urine examinations, electrocardiogram, cerebral computed tomography scan, and a chest film were used to screen each patient's general medical conditions. Premedication included atropine sulphate (0.5 mg i.v.), propofol (1.0 mg/kg i.v.), vecronium (0.5–1.0 mg i.v.), and succinylcholine (1.0 mg/kg i.v.) for each subject. ECT was performed between 7:00 and 9:00 a.m. using a Thymatron TM DG (Somatics, Inc., Lake Bluff, IL, USA) with standard settings (Abrams et al., 1989) and a bipolar brief pulse square wave. The patients were given bilateral ECT. Two stimulus electrodes were placed over the left and right front-temporal scalp. ECT conditions were same for all patients (charge delivered max 504 mC, current 0.9A, frequency 10–70 Hz, pulse width 0.5 ms, duration max 8 s). During ECT, motor convulsions, electro-encephalogram, induced tachycardia and, if necessary, electromyogram were monitored. ECT was given 12 times (three times a week for four weeks). Patients were placed on drug treatment for at least one week before ECT and drug treatment was maintained during the entire study period. The antidepressants used and number of subjects being treated with each were paroxetine ($n=4$), milnacipran ($n=4$), clomipramine ($n=3$), sertraline ($n=3$), imipramine ($n=2$), amitriptyline ($n=1$) and sulpiride ($n=1$).

All blood samples were taken at 7:00 am before breakfast (at least 12 h after the last medication) before and one week after finishing 12 ECT sessions (i.e., five weeks after starting ECT). After the patient had been lying at rest overnight, 15 mL of venous blood was drawn with the patient in the supine position. The plasma and serum samples were quickly separated in a centrifuge (2000 g, 10 min, 4 °C) and stored at −80 °C until assay. The serum BDNF levels were measured using a BDNF Emax Immunoassay Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. In short, 96-well microplates were coated with anti-BDNF monoclonal antibody and incubated at 4 °C for 18 h. The plates were incubated in a blocking buffer for 1 h at room temperature. The samples diluted with assay buffer 100-times and the BDNF standards were kept at room temperature on a horizontal shaker for 2 h, followed by washing with the appropriate washing buffer. The plates were incubated with antihuman BDNF polyclonal antibody at room temperature for 2 h and washed with the washing buffer. The plates were then incubated with anti-IgY antibody conjugated to horseradish peroxidase for 1 h at room temperature, then incubated in peroxidase substrate and tetramethylbenzidine solution to induce a color reaction. The reaction was stopped with 1 mol/L hydrochloric acid. The absorbance at 450 nm was measured with an Emax automated microplate reader. The standard curve was linear from 5 pg/mL to 5000 pg/mL, and the detection limit was 5 pg/mL. The intra- and inter-assay coefficients of variation were 5% and 7%, respectively. The recovery rate of the exogenously added BDNF in the measured plasma samples exceeded 95%.

The plasma homovanillic acid (HVA) levels were analyzed by high-performance liquid chromatography with electrochemical detection (HPLC-ECD) according to the method of Yeung et al. (1996). In short, each cyano-bonded solid-phase extraction cartridge was preconditioned with methanol followed by glass-distilled water. To each cartridge were added 0.3 mL of plasma sample or standard was added with 0.1 mL of working internal standard solution (5 ng of 5-hydroxyindolecarboxylic acid in 0.01 M KH_2PO_4, pH 7.2). The samples were allowed to pass slowly through the cartridge under a mild vacuum (15 mm Hg), and the filtrate was collected. The cartridge was then washed with 0.2 mL of distilled water. The filtrate portions were combined and deproteinized with 1 mL of acetonitrile. After mixing by vortex and centrifugation (1760 g, 4 °C for 10 min), an aliquot (5 μL) of the supernatant was injected into the HPLC. The intra- and inter-assay coefficients of variation were 6% and 8%, respectively. The recovery rate was more than 80%.

The plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels were analyzed according to the method of Minegishi and Ishizaki (1984). In brief, the plasma was separated by centrifugation at 600 g at 4 °C. Extraction was performed under a vacuum using Bond-Elut columns prepacked with 100 mg of C18-bonded silica (40 μm) in a with 1 mL capacity disposable syringe. The columns, which were inserted into a vacuum chamber connected to an aspirator, were prepared by washing with a 1 mL methanol followed by 1 mL of water. After the addition of 50 μL of vanilly alcohol (internal standard equivalent to 5 ng/mL) to 1 mL of plasma, samples were applied to and passed through the columns, followed by 0.75 mL of water to rinse off both residual samples and to easily elute hydrophilic compounds. The adsorbed materials were eluted with 200 μL of methanol to a 0.1 M phosphate buffer (pH 4.8) mixture (40:60, v/v). A 20 μL portion of this solution was injected into the HPLC. The intra- and inter-assay coefficients of variation were 4% and 8%, respectively. The recovery rate was more than 80%.

Plasma NOx was measured by the Griess reaction as the nitrate concentration after nitrate reduction to nitrite (Fiddler, 1977). In brief, 50 μl of 1% sulfanilamide was added to the sample first, incubated for

Table 1
Blood levels of catecholamine metabolites, BDNF, and NOx before ECT, responders: patients whose scores of Ham-D decreased by 50% or more, non-responders: patients whose scores of Ham-D decreased by less than 50%, the values are mean ± SD

	Responders (n=12)	Non-responders (n=6)
Sex	6/6	3/3
Age	58.6 ± 13.9	62.4 ± 15.1
Ham-D	25.0 ± 8.2	20.6 ± 4.4
MHPG (before) (ng/mL)	8.3 ± 3.8	7.6 ± 6.2
HVA (before) (ng/mL)	9.7 ± 2.0*	6.1 ± 2.1
BDNF (before) (ng/mL)	7.9 ± 9.9	11.5 ± 11.0
NOx (before) (μM)	30.7 ± 18.1	54.6 ± 40.5

* p=0.018, compared with non-responders.

5–10 min, and 50 μl of 0.1% *N*-1-naphthylethylendiamine dihydrochloride was then added. The reaction was performed at room temperature for 5–10 min, and absorbance at 540 nm was measured using nitrite solution as a standard. Levels of plasma NOx are reported in micromoles per liter. The intra- and inter-assay coefficients of variation were 2% and 3%, respectively. All the measurements were performed in duplicate or triplicate for each experiment.

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.

1.2. Statistical analysis

Statistical analysis was performed by the use of the Wilcoxon test or the Mann–Whitney *U*-test to investigate changes in Ham-D scores, as well as changes in MHPG, HVA, NOx, and BDNF levels. The relationship between two variables was examined using Spearman's correlation coefficients. The level of significance was set at $p<0.05$.

2. Results

The Ham-D score was significantly decreased after the 12 ECT sessions (before ECT: 23.1 ± 4.5; five weeks after start of ECT: 10.3 ± 3.4) ($p<0.001$). We defined the responders as the patients whose Ham-D scores decreased by 50% or more, and the non-responders as those whose scores decreased less than 50%. Twelve of 18 (67%) were responders (five weeks after start of ECT). Six of 18 (33%) showed Ham-D scores of under 7 points (remissional state) at five weeks after start of ECT.

Compared to non-responders, responders had significantly higher baseline (before ECT) plasma levels of HVA, but not MHPG (Table 1).

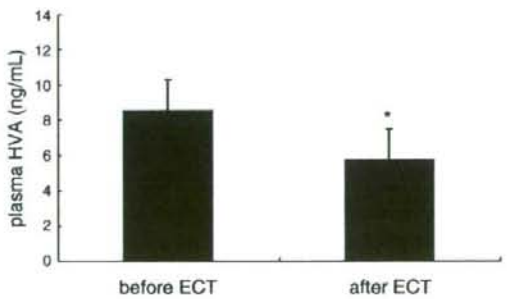

Fig. 1. Changes in plasma HVA levels before and after (i.e., five weeks after starting) ECT treatment (n=18). *p=0.008, compared with before ECT.

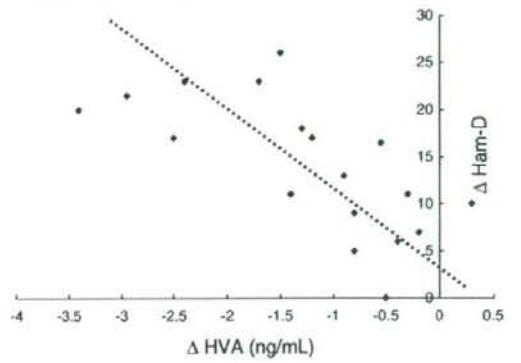

Fig. 2. Negative association between the changes in Ham-D and the changes in plasma HVA levels before and five weeks after start of ECT (n=18). rho=−0.620, p=0.0052.

Plasma HVA level was significantly decreased one week after finishing ECT treatment (five weeks after start of ECT) (before ECT: 8.5 ± 1.9 ng/mL; five weeks after start of ECT: 5.8 ± 2.2 ng/mL; p=0.008) (Fig. 1). However, no difference in plasma MHPG levels was found between before and after ECT treatment (before ECT: 8.1 ± 4.8 ng/mL; five weeks after start of ECT: 6.5 ± 5.1 ng/mL). A negative correlation was found between the changes in plasma HVA levels and the changes in Ham-D scores before and after ECT treatment (rho=−0.620, p=0.0052) (Fig. 2).

Serum BDNF levels were not increased one week after finishing ECT treatment (five weeks after start of ECT) (before ECT: 11.0 ± 11.2 ng/mL; 5 weeks after starting ECT: 11.0 ± 9.8 ng/mL) in all depressed patients. There was a significant increase of serum BDNF levels in responders (before ECT: 8.0 ± 9.7 ng/mL, five weeks after start of ECT: 15.1 ± 11.1 ng/mL; p=0.025), whereas serum BDNF levels in non-responders did not change (before ECT: 11.5 ± 11.0 ng/mL; five weeks after starting ECT: 9.4 ± 7.5 ng/mL) (Fig. 3). However, no correlations were found between the changes in serum BDNF levels and the changes in either Ham-D scores, or plasma levels of HVA, or MHPG from before to after ECT. Moreover, serum BDNF levels before ECT were not different between responders and non-responders (Table 1).

ECT did not alter plasma NOx levels (before ECT: 42.5 ± 35.7 μM; five weeks after start of ECT: 25.7 ± 16.7 μM, p=0.1909). In addition, plasma NOx levels before ECT were not different between responders and non-responders (Table 1).

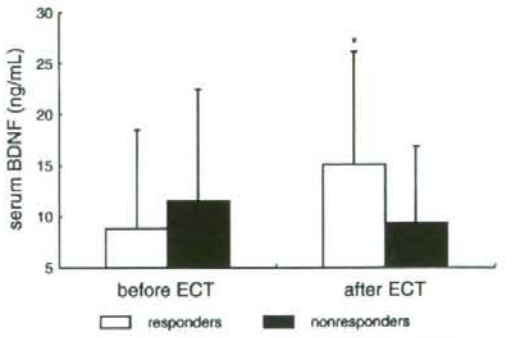

Fig. 3. Changes in serum BDNF levels before and after (i.e., five weeks after starting) ECT treatment in responders (n=12) and non-responders (n=6). Horizontal bar means median of the serum BDNF. *p=0.025, compared with before ECT.

3. Discussion

The present results reveal that ECT given to patients suffering from major depression increases serum BDNF levels in responders but not in non-responders. The present results are basically in accordance with previous reports that showed a regulation of peripheral BDNF levels in patients following ECT (Bocchio-Chiavetto et al., 2006; Marano et al., 2007). Thus, our results further support that this neurotrophin may play a role in the action of antidepressants (Karege et al., 2000a; Yoshimura et al., 2007). Marano et al. (2007) reported that 12 of 13 depressed patients who responded to ECT had an increase in plasma BDNF after their fourth ECT session. Bocchio-Chiavetto et al. (2006) demonstrated that serum BDNF levels were significantly increased one month after the end of ECT in antidepressant-refractory depressed patients. A longer duration of ECT may be needed to increase blood BDNF levels in refractory depressed patients. In the present study, we assessed the serum BDNF levels one week after finishing ECT (five weeks after starting ECT). It is possible that a longer treatment period is needed to elicit more robust increases in serum BDNF levels by ECT. In contrast to our findings, Gronli et al. (2007) found no significant changes in serum levels of nerve growth factor, BDNF, or neurotrophin-3 as a result of ECT. Nonetheless, it remains unclear how long it takes for ECT to increase peripheral BDNF levels. We recently demonstrated that eight weeks of treatment with paroxetine or milnacipran increased serum BDNF levels, whereas four weeks did not. In addition, responders to paroxetine or milnacipran had significantly higher serum BDNF levels after eight weeks of treatment compared to before treatment and to non-responders, in whom the levels were unchanged (Yoshimura et al., 2007). We have also reported that plasma BDNF levels were significantly increased in responders and partial responders, but not in non-responders, four weeks after repetitive transcranial magnetic stimulation (rTMS) treatment. In addition, we found an association between the changes in Ham-D scores and changes in plasma BDNF levels in all patients after rTMS treatment. These findings indicate that increased serum or plasma BDNF levels reflect improvement in the depressive state, regardless of the treatment type. Therefore, an increased serum or plasma BDNF level might be a biological state marker for recovering from depressive states via treatment with antidepressants, rTMS, or ECT. Moreover, rTMS or ECT most likely affects blood BDNF levels faster than antidepressants do.

The source of circulating BDNF remains unknown. Platelets, brain neurons, and vascular endothelial cells are currently considered to be putative sources. It was demonstrated that BDNF crosses the blood-brain barrier (Pan et al., 1998) and that BDNF levels in the brain and serum have been shown to undergo similar changes during the maturation and aging process in rats (Karege et al., 2002b). Furthermore, Lang et al. (2007) recently reported that serum BDNF concentrations reflect some aspects of neuronal plasticity, as indicated by the association of BDNF levels with those of *N*-acetylaspartate level in the cerebral cortex. These results indicate that blood BDNF levels might in part reflect the BDNF levels in the brain.

Another important finding of the present study was that ECT significantly reduced plasma HVA levels but not plasma MHPG levels, in parallel with the improvement of depressive symptoms. These results indicate that ECT's effects on dopaminergic neurons might be essentially associated with its clinical efficacy. We previously demonstrated that the levels of plasma MHPG, but not those of HVA, were significantly reduced after rTMS treatment, and that the change in plasma MHPG levels was negatively correlated with the change in scores of agitation. These findings suggest that noradrenergic neurons might be in part associated with the mechanisms for improving depressive state by rTMS (Yukimasa et al., 2006). Thus, it is possible that mechanisms of ECT's effect might be different from those of rTMS regarding the dynamics of catecholamines. In contrast, in several reports ECT increased, reduced, or did not alter cerebrospinal fluid or urinary monoamime metabolites levels (Jori et al., 1975; Harnryd et al., 1979; Lerer and Belmarker, 1982; Aberg-Wistedt et al., 1986; Lykouras et al., 1990). In addition, Linnoila et al. (1984) found no consistent change in plasma MHPG or plasma HVA, either acutely following seizure induction or at the end of the ECT course. Devanand et al. (1989) also failed to find significant ECT-induced acute or subacute changes in plasma MHPG or HVA. Taken together, these findings indicate that ECT's effect on catecholaminergic neurons remains controversial.

Depression is considered as a heterogeneous disorder consisting of various symptoms, which may be associated with the inconsistent results regarding ECT's effects on monoaminergic neurons. We previously demonstrated that depressed patients might be dichotomized into two groups; one characterized by anxiety, agitation, and/or hypochondriasis with high plasma MHPG levels, and the other by psychomotor retardation with low MHPG and/or HVA levels (Ueda et al., 2002; Shinkai et al., 2004). We also found a correlation between scores of agitation and/or anxiety in Ham-D and plasma levels of MHPG in 87 patients with major depressive disorder, indicating that depressed patients who predominantly exhibited agitation/anxiety were characterized by higher plasma MHPG levels (Yoshimura et al., 2004). In addition, we have also reported that patients with psychotic depression (depression with psychotic features) had higher plasma HVA levels, and combined treatment using antidepressants or mood stabilizers with atypical antipsychotic drugs decreased plasma HVA levels in parallel with improvement of depressive symptoms (Goto et al., 2006). Interestingly, in the present study, five of 18 patients were diagnosed as having major depressive episodes with psychotic features, all of whom responded to ECT. In regards to the association between BDNF and dopamine, Marano et al. (2007) reported that the presence of psychosis was associated with a greater percent increase in plasma BDNF, suggesting that patients with psychotic depression are particularly responsive to ECT. Taking those findings into account, it is plausible that hyper-dopaminergic activity might suppress the synthesis of BDNF, and ECT might affect the BDNF levels by reducing the dopaminergic activity. Indeed, Noh et al. (1999) demonstrated *in vitro* that both excessive and low catecholamine levels decrease neurosynthesis.

The ubiquitous free radical NO has a wide variety of roles in the central nervous system (Rosen et al., 2003). It acts as a neurotransmitter, a neuromodulator and an intraneuronal second-messenger, and both an anti- and pro-apoptotic activator (Rosen et al., 2003). Current research validates NO's ability to diffuse to adjacent neurons, thereby participating in non-synaptic diffusion neurotransmission. Several NO production factors have been implicated in the regulation of cerebral vascular tone at several levels. Endothelial NO (eNOS) is an important factor of cerebral blood flow. Decreased cerebral blood flow in the anterofrontal lobe as well as its recovery after ECT were reported in depressed patients (Navarro et al., 2004). Moreover, Chrapko et al. (2004) reported that the levels of both plasma NOx and platelet eNOS activity were significantly lower in subjects with major depressive disorder when compared to healthy controls. The authors also found that treatment with antidepressants increased these parameters in depressed patients (Chrapko et al., 2006). We thus speculated that ECT influenced the plasma NOx level. In the present study, however, we could not find an increase in this level after ECT, suggesting that NO might not be strongly involved in the mechanisms underlying ECT's effect.

In conclusion, we found in all patients a significant decrease in plasma HVA levels, but not plasma MHPG levels or plasma NOx levels as well as a significant increase in serum BDNF levels in responders to ECT. However, in non-responders, ECT did not change serum BDNF levels. The present findings suggest that the mechanisms of ECT in treatment-refractory depression may be in part related to dopaminergic neurons and BDNF.

We are aware of the limitation of the present study. Our sample size was very small and heterogeneous, which prevented us from obtaining informative results for response to treatment. Plasma levels of

catecholamine metabolites, NOx and serum BDNF levels appear to be partially derived from central sources (Yoshimura et al., 2004, 2007). In other words, blood levels of catecholamine metabolites, BDNF, and NOx only partially reflect the activities of the neurons in the brain. Serum BDNF levels are approximately 100 to 250 times greater than platelet-poor plasma. Platelets are the major source of serum BDNF, as they sequester large quantities of it in order to release during clotting. Sources of circulating plasma BDNF include vascular endothelial cells as well as the brain (Lommatzsch et al., 2005). Platelets have a life span of approximately 10 days (Harker et al., 2000), whereas, plasma BDNF turnover is completed about every 6 min (Podusto et al., 1996). Therefore, because it is minimally affected by the amount stored in platelets, plasma BDNF is likely to be a more suitable index of brain BDNF levels (Marano et al., 2007). Nonetheless, it remains unclear to what extent peripheral levels reflect brain levels of BDNF.

The most serious limitation in the present study was that there was no control group without ECT (the sham controlled group). This makes it difficult to attribute the improvements of Ham-D to ECT rather than to a placebo response. In addition, all of the patients were taking antidepressants, and neurochemical changes are not incompatible with a placebo effect, as imaging findings in depressed patients have shown that the clinical improvement following placebo treatment was substantiated by regional metabolic changes in the cortical and subcortical regions. Thus, definitively attributing the behavioral or neurochemical changes to ECT is not possible until these results are replicated in a controlled fashion. In addition, we combined the use of antidepressants with ECT, and hence these drugs may have affected plasma levels of catecholamine metabolites and NOx as well as serum BDNF levels. Therefore, further study will be needed to confirm these preliminary findings.

Acknowledgements

Authors gratefully thank Dr. Takashi Terao (Professor and Chairman at Department of Psychiatry of Oita University School of Medicine) for instructing the techniques of ECT. This study was supported by a grant from Iryo-Kaigo-Kyoiku-Kenkyu Zaidan and Grants-in-Aid for Science Research in Japan.

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Acta Psychiatr Scand 2008: 117: 35–40
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DOI: 10.1111/j.1600-0447.2007.01119.x

ACTA PSYCHIATRICA SCANDINAVICA

Definitions of recovery and outcomes of major depression: results from a 10-year follow-up

Furukawa TA, Fujita A, Harai H, Yoshimura R, Kitamura T, Takahashi K. Definitions of recovery and outcomes of major depression: results from a 10-year follow-up.

Objective: Consensus operational definitions for symptomatic remission and recovery of a major depressive episode have been proposed but only irregularly followed.
Method: We examined the predictive validity of different definitions of recovery in a multi-center 10-year follow-up study of an inception cohort of untreated unipolar major depressive episodes ($n = 95$). Time to recovery and time to recurrence after recovery were estimated by Kaplan–Meier survival analyses for alternative definitions requiring 2, 4, 6 or 12 months of remission to declare recovery.
Results: The median time to recovery was 3.0, 4.0, 4.0 and 12.0 months respectively. The index episode lasted longer than 24 months in 9.4%, 9.2%, 12.6% and 24.5%. The median time to subthreshold recurrence was 16.0, 32.0, 42.0 and 74.0 months.
Conclusion: Either 4- or 6-month duration of remission defined a change point before which the episode was continuous and after which the recurrence was reasonably unlikely.

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Key words: depressive disorder; diagnostic criteria; remission; recovery

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Accepted for publication October 3, 2007

Significant outcomes

- Requiring two months of remission is probably too short to declare recovery because a subthreshold recurrence occurs in more than half of the cohort within a year and a half.
- If we require 4 or 6 months before we declare recovery, the median time to recovery is 4 months and that to subthreshold recurrence is nearly 3 years.
- Requiring 12 months of remission before declaring recovery would make the episode discontinuous yet long and inflate the rate of chronicity.

Limitations

- The sample size was relatively small and the confidence intervals were accordingly wide.
- This was a naturalistic study and the treatments were not controlled.
- Validity of alternative definitions of remission requires a separate study.

Introduction

Confusions and inconsistencies persist in the literature with regard to operational definitions of critical change points in the course of a major depressive episode, such as remission, recovery, relapse and recurrence. It was the US NIMH Collaborative Depression Study (CDS), a landmark long-term cohort study of patients with mood disorder, that first operationalized remission as a state with no more than one or two mild depressive criterion symptoms, and recovery as

eight or more weeks of remission (1). Some have followed this convention (2–5), while others have not (6–9). But none of these studies has provided empirical examination of the validity of competing definitions.

With regard to the official diagnostic criteria, the definitions in DSM-IV are in line with the CDS definitions because they declare 'recovery' if 'full remission', which is defined as a period of at least 2 months in which there are not significant symptoms of mania or depression, is attained between two mood episodes (10). The ICD-10 also appears to follow this tradition when it requires 'at least 2 months free from any significant mood symptoms' for depressive disorder to be recurrent (11). On the other hand, the DSM-III-R was somewhat aberrant because it required 'no significant signs or symptoms of the disturbance for at least 6 months' for an episode to be in full remission, while requiring '2 months of return to more or less usual functioning' for the disorder to be recurrent (12). The DSM-III did not have any explicit definitions for recurrence or remission (13).

This state of confusion is unfortunate not only for the psychiatric sciences because then findings cannot be compared and accumulated, but also for the psychiatric services because then the literature cannot inform the practitioners about how to judge recovery and declare the end of continuation treatment or about whether to recommend maintenance treatment based on knowledge of likelihood of recurrence.

It is important to note that, in this framework for long-term treatment of depression (14, 15), emphasis is placed on the symptomatic aspects of the course of a major depressive episode. This is in line with recent definitions of remission in psychotic disorders (16, 17) and anxiety disorders (18). However, there is growing tendency, especially with regard to schizophrenia and other serious mental disorders, to use the term 'recovery' in conjunction with quality and meaning of life in spite of continued symptoms (19). Whether we need to include functional or even broader normalization in the definition of recovery with regard to depression is being discussed and researched (20), but in this article, we follow the symptomatological orientation currently adopted in the mood disorder section of the DSM-IV (10) and ICD-10 (11).

Aims of the study

The present article therefore sets out to examine the differential predictive validity of the competing definitions of symptomatic recovery. We propose that a more valid definition of recovery should define a change point until which the syndrome is relatively continuous, but after which a return of the syndrome will become reasonably unlikely.

Material and methods

Data for this report come from the Group for Longitudinal Affective Disorders Study (GLADS), described in detail elsewhere (5, 21). Briefly, it is a multi-center collaborative naturalistic study of patients with heretofore untreated mood episodes who had presented to various psychiatric facilities all over Japan.

The 23 collaborating centers included psychiatric departments of 13 university hospitals and six general hospitals, three mental hospitals and one community mental health center. Participating psychiatrists at each center administered a semi-structured interview, called the Psychiatric Initial Screening for Affective Disorders (PISA) (22) to a representative subset of its first-visit patients to ascertain the patient's eligibility. The details of the predetermined rules on how to select a subset of first-visit patients were left to individual centers, depending on their human and logistic resources: some centers administered PISA to all their first-visit patients, others did so with those on a certain day of the week and still others did so with those seen by one or two collaborating psychiatrists only. The eligibility criteria were: i) depressive state or manic state; ii) having received no antidepressant or antipsychotic medication in the preceding 3 months; iii) aged 18 years or older; and iv) absence of conditions that would render detailed psychopathological assessment difficult. Out of all the eligible subjects, each participating center was expected to enter the first such patient every 1 or 2 months.

The study protocol was approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan, as well as those of the participating centers. Written informed consent was obtained from all participants after full disclosure of the purposes and procedures of the study. The patients eligible for and consenting to the study were then interviewed within 1 week of entry by a psychiatrist using the entry version of the Comprehensive Assessment List for Affective Disorders (COALA) (23). The COALA consists of a series of semi-structured interviews that enable serial assessment of the cohort; these include the entry version, monthly follow-up

version, 6-monthly follow-up version and yearly follow-up version. The reliability of the PISA and COALA has been reported to be good to excellent (24). The cohort was followed up monthly until treatment termination, 6-monthly thereafter up to 2 years and then annually up to 10 years. At each assessment, the course of the illness was recorded for each month of the survey period in five grades of 5 = above diagnostic threshold for major depressive episode, 4 = between 5 and 3, 3 = asymptomatic or minimally symptomatic with at most two of nine diagnostic criteria symptoms of at most mild degree, 2 = between 3 and 1 and 1 = above diagnostic threshold for manic episode.

The present paper focuses on the course of the subset of the cohort who were diagnosed with major depressive disorder according to DSM-IV (10). We defined remission in accordance with the NIMH CDS as a state with no more than one or two mild criterion depressive symptoms (2). The CDS then defined recovery as consecutive two months of remission. Once recovery was declared, patients were considered to have fallen into a new mood episode (recurrence) when they met the DSM-IV criteria for major depressive episode, manic episode or hypomanic episode. In addition, if they did not yet meet the criteria for a major depressive episode but had more than two symptoms or had only one or two symptoms that were graver than mild degree for a month, they were considered to have fallen into a 'subthreshold' depressive episode. The duration of the well interval was counted after the end of the period required for judging recovery.

The CDS definition of recovery by 2 months of remission has been criticized for being too short (25, 26) and the consensus definitions proposed alternative definitions of recovery by 4 or 6 months of remission. The present paper examines the predictive validity of alternative duration requirements of 2, 4, 6 and 12 months of remission to define recovery. We hypothesized that a more valid definition of duration required for declaring recovery would:

i) not prolong the duration of the index episode too much, lest the episode contains too long well periods in itself;
ii) not increase the rates of chronicity (never attaining recovery) too much, lest we give an overly pessimistic impression that depression is a chronic or incurable disease;
iii) ensure that the time to recurrence is reasonably long, so that 'recovery' once declared can assure the patients that a return of symptoms is reasonably unlikely.

We used the SPSS for Windows 11.5 (27) to perform Kaplan–Meier analyses to depict survival curves of the major depressive episodes.

Results

A total of 1853 patients were screened at 23 participating centers between December 1992 and December 1995. A total of 466 patients suffered from broadly defined mood disorders, but either failed to meet the other entry criteria or declined consent and 126 entered the study. Of these, 95 met the DSM-IV criteria for major depressive disorder, either single episode (n = 67, 71%) or recurrent (n = 28, 29%). Fifty-six subjects (59%) were females, and the mean age was 44.3 (SD 15.2). The mean score for the 17-item Hamilton Rating Scale for Depression was 19.9 (SD 8.6) and 14 (15%) were inpatients upon study entry. The major depressive episode was superimposed on pre-existing dysthymia in five (5%). The median length of episode before study entry was 3.0 months (range: 0.5–48.0).

Table 1 gives the median duration of the index episode and rates of chronicity at 12, 24, 60 and 120 months, depending on the numbers of months of remission required to declare recovery. The table also gives the median time to recurrence of a full episode or a subthreshold episode after recovery

Table 1. Outcomes of major depressive episodes for different definitions of recovery

Definition of recovery	Follow-up rate (%)	Median duration of index episode (months)	Rates of chronicity (%)				Median length of well interval (months)	
			12-month	24-month	60-month	120-month	Until full episode recurrence	Until subthreshold recurrence
2 months of remission	90.5	3.0 (2.3–3.7)	16.4	9.4	5.4	3.6	103†	17.0 (1.9–32.1)
4 months of remission	89.5	4.0 (2.9–5.1)	21.9	9.2	6.2	4.1	>101‡	32.0 (1.6–62.4)
6 months of remission	88.4	4.0 (2.2–5.8)	29.9	12.6	6.3	4.2	113 (62–164)	47.0 (10.4–83.6)
12 months of remission	82.1	12.0 (7.9–16.1)	46.0	24.5	12.7	5.1	97†	74.0†

Numbers in parentheses represent 95% confidence intervals.
†95% confidence intervals could not be calculated.
‡The cumulative rate of relapse at the latest follow-up of 112 months was 53.2%, so that the median can be estimated to be close to 120.

was declared, according to each proposed definition.

We illustrate the actual numbers of patients reaching each critical change points or being lost before reaching one in the case of the operational definition of recovery requiring 6 months of remission. Of the original cohort of 95 patients, 84 patients reached recovery so defined, 10 patients were lost to follow-up before reaching recovery and one never experienced recovery over the entire 120 months of follow-up. Of these 84 who were judged recovered, 10 never had a recurrence until the end of the 120-month follow-up, 29 experienced a full episode recurrence, additional 11 experienced a subthreshold recurrence and one presented with a manic episode, 33 were lost to follow-up without ever recording any of these events. Because this was a naturalistic follow-up study and the treatment was not controlled, around the time of recovery, the patients were receiving on average 45.1 (SD 64.7, IQR 0–60) mg/day of imipramine equivalent and only 16 (19%) were on >75 mg/day.

Discussion

This is the first study to examine the predictive validity of different duration requirements of remission to achieve recovery in terms of the length of the index episode, rates of chronicity and the succeeding well interval until recurrence, based on a long-term naturalistic follow-up data. We found that different definitions can give up to fourfold differences in estimates of episode length and time to subthreshold recurrence but not in time to full recurrence.

Several recent studies have shown that subthreshold depression is associated with psychosocial disability and more severe future course of the illness and requires treatment (28, 29). A systematic review of continuing antidepressant treatment after acute phase treatment reported a consistent relative risk reduction of about 50% in relapse rates up to 3 years (30). For a representative patient in our cohort, then, even if recovery is achieved after 2 months of remission, continuing adequate antidepressant treatment for 1½ years would reduce the subthreshold recurrence rates from 50% to 25%; an average patient may then very well wish to stay on medication. On the other hand, if recovery is declared after 4 or 6 months of remission, one needs to be on medication for 3–4 years to reduce the subthreshold recurrence rates from 50% to 25%; many if not all the patients may choose to stop the medication.

Given our hypotheses regarding the predictive validity of the operational definition of recovery, requiring 12 months would include so much well time before recovery is declared as to draw an unnecessarily chronic picture for the index episode. Requiring only 2 months, on the other hand, would devaluate the significance of recovery because half of the patients so declared would experience a subthreshold recurrence within 1½ years. It is noteworthy that the time to full recurrence remained constant at about 100 months for the three definitions examined. However, given the clinical significance of subthreshold depression noted above, requiring 4- to 6-month remission before declaring recovery appears to be a reasonable definition, as it would not make the index episode unnecessarily chronic, yet assures a relatively low likelihood of subthreshold recurrence once recovery is declared and can provide some indication for ensuing treatments.

There are some possible weaknesses of the present study. First, the sample size was relatively small and 95% confidence intervals were sometimes incalculable or very wide, especially with regard to time to full episode recurrence. This may partly explain the apparent lack of differentiation among various definitions of recovery with regard to this variable. Secondly, this was a naturalistic study, in which we did not control the treatment, and the amount of treatment, actually provided was very low. During the continuation phase, 43% were not receiving any antidepressant therapy and a further 37% were on inadequate treatment with <75 mg/day of imipramine equivalent or <600 mg/day of lithium. Six months later, during the maintenance phase, the corresponding figures were 50% and 29% (31). Thirdly, our cohort consisted mainly of first episode patients and with less severe symptomatology, and this may have influenced estimates of time to recurrence and may be another reason for lack of difference in times to full episode recurrence among various definitions of recovery that we examined. However, Cox regression analyses did not reveal statistically significant influence of recurrent vs. single episode in the median durations of the index episode or the median lengths of the ensuing well intervals. It would be interesting to see analyses similar to ours with the data available from other long-term studies of more severe, recurrent cohorts. Finally, we could not examine the influence of different definitions of remission. One study clearly pointed to the importance of this definition because different symptomatological cut-offs to define remission resulted in an almost sevenfold increase in the length of a depressive episode (32). There are also

arguments for including more than symptomatic criteria to define remission (33). These problems need separate examination.

The greatest strength of the current study, on the other hand, is the high follow-up rates achieved through serial assessments of a prospective cohort for 10 years. Some drop-outs were inevitable and we adjusted for the censored cases through survival analyses. The current DSM-IV follows the NIMH CDS tradition and requires 2 months of no significant signs or symptoms of the disturbance before declaring 'full remission'. The naturalistic follow-up data given in the present report along with the functional and prognostic significance of subthreshold depression demonstrated in cross-sectional and longitudinal studies (28), and the experimental treatment data summarized in the meta-analysis (30) warrant reconsideration of the consensus definitions of remission, recovery, relapse and recurrence in major depression for the upcoming DSM-V.

Acknowledgements

This paper was prepared on behalf of the GLADS. This study was supported by Research Grants 3A-6, 6A-4, 8B-2, 11A-5, 14A-3 and 17A-5 for Nervous and Mental Disorders from the Ministry of Health, Labor and Welfare, Japan.

Dr. Furukawa reports that he has received research grants from Dai-Nippon-Sumitomo, GlaxoSmithKline, Janssen, Meiji and Pfizer, and speaking fees from Astellas, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, Organon, Pfizer and Yoshitomi.

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BJPsych | The British Journal of Psychiatry (2009) 194, 1–2. doi: 10.1192/bjp.bp.108.055798

AUTHOR'S PROOF

Short report

Lithium levels in drinking water and reduced risk of suicide

Hirochika Ohgami, Takeshi Terao, Ippei Shiotsuki, Nobuyoshi Ishii and Noboru Iwata

Summary

Although lithium is known to prevent suicide in people with mood disorders, it is uncertain whether lithium in drinking water could also help lower the risk in the general population. To investigate this, we examined lithium levels in tap water in the 18 municipalities of Oita prefecture in Japan in relation to the suicide standardised mortality ratio (SMR) in each municipality. We found that lithium levels were significantly and negatively associated with SMR averages for 2002–2006. These findings suggest that even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population.

Declaration of interest

None.

Author: This suggests that by taking lithium, suicide can be stopped altogether. Suggest rephrase to 'Although long-term treatment with lithium is known to lower suicide risk in people with mood disorders, . . .' (Column 1) (AQ1)

Author: Added to clarify (Column 2) (AQ2)

Author: Implies that suicide can be stopped altogether. Suggest rephrase to ' . . . is effective in lowering the risk of suicide.' Please note that I have substituted 'prevent' to 'reduced/ lowered the risk' throughout the article rem this point. Please check that OK. (Column 1) (AQ3)

There is increasing evidence that lithium is effective in preventing suicide. Several meta-analyses have shown antisuicidal effects of lithium[1–3] in people with mood disorders, namely major depression and bipolar disorder, but these studies have reviewed only randomised controlled trials primarily comparing lithium with placebo or other drugs in long-term prophylactic treatment which were maintained at so-called therapeutic levels. The potential benefits of low levels of lithium in reducing the risk of suicide have not been widely investigated; however, at least one study has suggested that very low levels of lithium in drinking water could have lowered the risk of suicide in Texas.[4] In this study, lithium levels in the drinking water of 27 Texas counties were arbitrarily divided into (relatively) high (70–160 μg/l), moderate (13–60 μg/l) and low (0–12 μg/l) areas.[4] The authors reported suicide rates of 8.7 per 100 000 of population in the (relatively) high lithium area, 14.8 in the moderate lithium area and 14.2 in the low lithium area.[4] Although it cannot be denied that such arbitrary division may have detected a spurious association between lithium and reduced risk of suicide, the findings are intriguing. Unfortunately, until now, no further studies have been conducted that could confirm or reject their findings.

In our study, lithium levels in drinking water (tap water) of all the municipalities of Oita prefecture, an average (economically, culturally, and politically) prefecture in Japan, are used to investigate the association with suicide rates in each municipality. In contrast to the Texas study,[4] lithium levels are used as a continuous value in order to exclude the potential for a spurious finding resulting from the arbitrary division of lithium levels.

Method

In 2006, the population of Oita prefecture was 1 206 174. Oita has 18 cities, towns and villages. Of the 18 municipalities, Oita city had the largest population (463 973; 38%) while populations of other city centrer ranged from 126 781 (Beppu city) to 2408 (Hime-shima village). Thus, the difference of population is very large across the 18 municipalities.

By taking the difference in gender and age distribution of individual city populations into account, the standardised mortality ratio (SMR) of suicide was calculated for each individual city. The SMR is an indirect method of adjusting a mortality rate, defined as the number of observed deaths in an individual city population divided by the number of expected deaths compared with the gender- and age-matched general population. We examined Japanese government statistics on suicide in Oita prefecture and used them as the average suicide SMR for 5 years, 2002–2006, across all the 18 municipalities.

Lithium levels in the tap water suppliers of each municipality were measured by using ion chromatography at Oita City Waterworks Bureau or by using mass spectroscopy at Oita Yakuzaishi Kensa Center. Both methods can measure very small amounts of lithium; the minimal amount of lithium which can be measured is 0.1 ppb (0.1 μg/l). If lithium levels of drinking water were measured at multiple water suppliers in the same municipality, the mean value was calculated. Although lithium levels were measured once, we confirmed a very small fluctuation in levels because the correlation coefficient between the lithium levels and those remeasured after 1 year in the same places was 0.998.

The distribution of lithium levels was considerably skewed (skewness=3.39; kurtosis=12.80). We thus employed log-transformation (skewness=0.002; kurtosis=0.075) in order to use parametric statistical procedures. Because of greater differences in population size across the 18 municipalities, weighted least squares regression analysis adjusted for the size of each population was used to investigate the association of lithium levels in drinking water and the SMRs.

Results

In 2006, the lithium levels in drinking water of 18 municipalities of Oita ranged from 0.7 to 59 μg/l. In total, the average suicide SMR in Oita for 2002–2006 was 105 (range 60–181), which corresponds well with the average SMR for Japan (100). The SMRs of suicide across the 18 municipalities were significantly and negatively associated with lithium levels ($\beta = -0.65$, $P < 0.004$) (Fig. 1). The significant association remained in males ($\beta = -0.61$, $P < 0.008$) and a marginal significance was found in females ($\beta = -0.46$, $0.05 < P < 0.06$).

Discussion

In the present study, lithium levels were significantly and negatively associated with the SMRs across 18 municipalities. These findings suggest that even very low lithium levels may reduce the risk of suicide and that within the levels there is a dose–response relationship. Although it seems unlikely that such low lithium levels can bring about mood-stabilising effects and

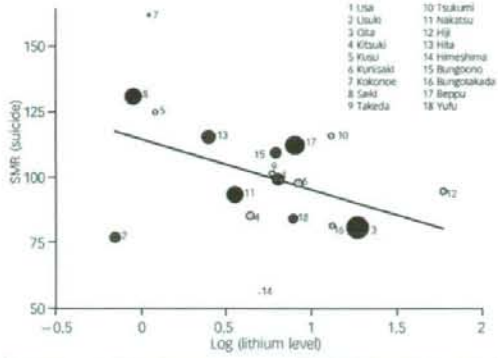

Fig. 1 Lithium levels in drinking water and the average suicide standardised mortality ratio (SMR) for 2002–2006 in 18 municipalities of Oita prefecture.

The lithium level is log-transformed and the size of the dot represents population size. The SMRs of suicide across 18 municipalities were significantly and negatively associated with the lithium levels ($\beta = -0.65$, $P < 0.004$).

thereby prevent suicide, could the antisuicidal effect of lithium be unrelated to its prophylactic effect for mood disorders? Müller-Oelinghausen *et al*[5] revealed that a significant reduction in suicide attempts occurred even in poor responders to lithium prophylaxis for mood disorders. Therefore, it seems probable that the antisuicidal effect of lithium may be unrelated to the mood-stabilising effects and that very low lithium levels may possess an antisuicidal effect. On the other hand, although lithium levels are extremely low in the drinking water, long-term exposure to lithium may be a factor which mitigates low absolute levels. It can be speculated that very low but very long lithium exposure can enhance neurotrophic factors, neuroprotective factors and/or neurogenesis, which may account for a reduced risk of suicide.

The limitations of the present study are as follows. First, although Oita prefecture is demographically average in Japan, the present findings were derived from a local prefecture and therefore only limited generalisation is possible. Second, other factors such as psychosocial and economical factors were not taken into consideration.

In conclusion, our study suggests that very low lithium in drinking water can lower the risk of suicide. Further studies are required to confirm this possibility and extrapolate it to other countries.

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First received 5 Jun 2008, final revision 28 Sep 2008, accepted 23 Oct 2008

Author: Please provide qualifications for all authors of the study (Column 2) (AQ5)

Acknowledgements

We thank Oita City Waterworks Bureau and Oita Yakuzaishi Kensa Center for measuring lithium levels.

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INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry (2008)
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/gps.1980

Changes in regional cerebral blood flow following antidepressant treatment in late-life depression

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SUMMARY

Objective Reversible/irreversible abnormalities of regional cerebral blood flow (rCBF) are seen in patients with depression. However, in late-life depression there is little evidence of a longitudinal change in rCBF through remission. We examined whether the decreased rCBF in individuals with late-life depression resolves following treatment.

Methods Twenty-five depressed patients older than 55 years completed the Hamilton Rating Scale for Depression and single photon emission computed tomography before and after a mean of 13.7 weeks of pharmacotherapy. Quantitative analyses were performed using the Statistical Parametric Mapping procedure.

Results Patients with depression demonstrated decreased rCBF in the anterior ventral and dorsal medial prefrontal cortex (PFC), including anterior cingulate cortices, bilateral ventrolateral PFC to temporal cortices, and bilateral medial to lateral parieto-occipital lobes relative to healthy controls. No particular areas showed increased rCBF. Following pharmacotherapy, rCBF significantly increased in the left dorsolateral PFC to precentral areas and the right parieto-occipital regions. However, decreased rCBF at baseline in the anterior ventral/dorsal medial PFC, bilateral ventrolateral PFC, bilateral temporal lobes, and bilateral parietal lobes did not show significant improvement after treatment.

Conclusions Remarkable improvements in rCBF in the left dorsolateral PFC to precentral regions are consistent with the hypothesis that neuronetworks including the left frontal cortex may be functionally and reversibly involved in late-life unipolar major depression (state-dependent). In contrast, neural circuits including bilateral medial, dorsolateral, and parietal areas may reflect underlying and continuous pathognomonic brain dysfunction of depression (trait-dependent). Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — vascular depression; late-life; SPECT; frontal lobe

INTRODUCTION

A number of functional neuroimaging studies, including positron emission tomography (PET) and single photon emission computed tomography (SPECT), demonstrate focal or diffuse cerebral dysfunction in individuals with depression. On one hand, studies have documented an overall decrease in hemispheric mean cerebral blood flow (CBF) and/or rate of glucose metabolism in depression (Lesser *et al.*, 1994; Kocmur *et al.*, 1998). On the other hand, studies report a decrease/increase in regional CBF (rCBF) and/or glucose metabolism in particular regions of the brain. Such regions include the prefrontal cortex (PFC), cingulate, amygdala/hippocampus, basal ganglia, or thalamus, suggesting involvement of the networks that regulate mood and emotion (Buchsbaum *et al.*, 1986; Curran *et al.*, 1993; Dolan *et al.*, 1993; Bench *et al.*, 1995; Lesser *et al.*, 1994; Goodwin, 1997; Mayberg *et al.*, 1999; Nobler *et al.*, 2000; Anand and Shekhar, 2003; Navarro *et al.*, 2004). Although results of studies are inconsistent, most research focuses on dysfunction of mood-related circuits involving the multiple prefrontal cortices and limbic structures. For example, Baxster *et al.* (1989) used PET and reported

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Received 13 April 2007
Accepted 27 November 2007

that glucose metabolic rates of patients with depression were significantly lower than those in healthy controls in the left anterior dorsolateral PFC. Mayberg *et al.* (1994) reported that patients with severe unipolar depression demonstrated significant CBF decreases in the bilateral frontal cortices, anterior temporal cortices, anterior cingulate cortices (ACC), and caudate compared with healthy controls. The greatest decrease was seen in the paralimbic regions, specifically in the inferior frontal lobe and ACC.

Much less is known concerning the longitudinal changes in CBF/glucose metabolism in depression. Some studies demonstrate that the decrease in rCBF observed during a depressive episode is reversible and recovers to a level comparable with healthy subjects, suggesting that changes in rCBF are disease-state dependent (Baxter *et al.*, 1989; Goodwin *et al.*, 1993; Mayberg *et al.*, 1994; Buchsbaum *et al.*, 1997; Brody *et al.*, 1999; Mayberg *et al.*, 1999, 2000, 2002). Bench *et al.* (1995) reported patterns of change in rCBF following clinical remission of depression. Remission was associated with a significant increase in rCBF in the left dorsolateral and medial PFC, including the ACC. Researchers have also suggested that unmedicated subjects with depression showed increased rCBF/metabolism, which decreased with effective antidepressant treatments (Buchsbaum *et al.*, 1997; Drevets, 1999; Mayberg *et al.*, 1999).

On the other hand, decreased rCBF observed in the anterior PFC and left amygdala areas has been shown to remain at a lower level compared with healthy subjects, suggesting trait-dependent abnormalities (Drevets *et al.*, 1992). Recent functional activation studies using a transient mood challenge revealed that patients in remission from depression still show rCBF decreases in the pregenual ACC (Liotti *et al.*, 2002). These persistent decreases may suggest a potential depression trait marker independent of clinical illness status.

Additionally, elderly patients with depression may frequently show multiple small lacunae/cerebrovascular lesions. In 1997, Krishnan *et al.* and Alexopoulos *et al.* proposed the term 'vascular depression' to categorize this subtype of depression occurring in the context of cerebrovascular disease. Although most CBF studies of depression have been confined to depression without cerebrovascular changes (Goodwin *et al.*, 1993; Bench *et al.*, 1995), the above-mentioned network activities would likely be enhanced in vascular depression secondary to frontal-subcortical disconnections. Individuals with late-life and young depression have been reported to show similar longitudinal time-course changes of rCBF in general. However, areas showing rCBF improvement are inconsistent. Navarro *et al.* (2002) found that the left frontal hypoperfusion in elderly depressed patients disappeared during remission; supporting the hypothesis that neuronetworks involving the left frontal cortex may be functionally and reversibly involved in late-life unipolar major depression. Kimura *et al.* (2003) reported the result that in vascular depression left anterior frontal rCBF was lower in both depressed and remitted states compared to non-vascular depression. This finding might not only represent a trait marker, but also correlate with the duration of disease and likelihood of recurrence and relapse.

The main aim of our study is to make sure where in brain CBF abnormality would change and assess the relation between essential brain abnormalities and depressive symptoms with late-life depression.

METHODS

Participants

Twenty-five elderly inpatients or outpatients (3 men and 22 women) aged 55 years or older (age = 70.4 ± 7.5 years) were included in this study. All the patients were right-handed. Inclusion criteria were Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for major depressive disorder. No one had a history of any other major psychiatric disorders. In addition, patients with neurological diseases including apparent cerebrovascular events and degenerative disorders were excluded.

Table 1. Demographic variables and characteristics of the participants

	$N = 25$
Sex, female %	88.0
Education, years	11.4 (3.5)
Age, years	
Onset of the first depressive episode	62.0 (12.0)
Time at examination	70.4 (7.5)
Number of depressive episodes	2.4 (2.0)
Single episode %	44.0
Pharmacotherapy %, Equivalent imipramine mg/day	
Paroxetine	32, 104.8 (39.5)
Milnacipran	40, 94.9 (54.3)
Tricylic antidepressants	28, 112.2 (56.4)
HRSD score	22.6 (6.0)
MMSE score	27.0 (2.8)
Hachinski score	3.7 (1.6)

Data are expressed as mean (SD) unless otherwise indicated.
HRSD = Hamilton Rating Scale for Depression; MMSE = Mini-Mental State Examination.

The demographic variables and characteristics of the patients are shown in Table 1. Depressive symptoms were rated using the Hamilton Rating Scale for Depression (HRSD), 21-item version (Hamilton, 1960) and overall cognitive function was measured by the Mini-Mental State Examination (MMSE). The mean HRSD and MMSE scores at baseline are presented in Table 1. As is indexed by MMSE, no participants suffered from comorbid dementia. Each participant's vascular risk factors were assessed using Hachinski ischaemia scores (Hachinski *et al.*, 1975), which ranged from 2–8 points.

This study was approved by the Ethics Committee of Showa University. All patients were antidepressant drug-naïve or off-medication at least 2 weeks before the start of the study. After the purpose of the study was fully explained, written informed consent was obtained from each participant. Magnetic resonance imaging (MRI) data were assessed using the modified Fazekas criteria (Greenwald *et al.*, 1996; Krishnan *et al.*, 1997). This criterion provided a rough assessment of the extent of subcortical gray matter, deep white matter, and periventricular changes on brain MRI. Based on this criterion, 12 participants were classified as having vascular lesions.

Pharmacological treatment and longitudinal assessment

All patients received pharmacotherapy with paroxetine, milnacipran, or tricyclic antidepressants at random. The mean maximum doses of paroxetine (23.8 ± 13.0 mg/day) and milnacipran (80.0 ± 23.0 mg/day) were the same in terms of imipramine equivalence. All the patients were well compliant with antidepressant treatment and experienced a significant clinical improvement in depressive symptoms as indexed by the second HRSD score <10 or less than a half of the baseline. After approximately 13.7 weeks' treatment, the mean HRSD score changed from 22.6 ± 6.0 at baseline to 8.7 ± 5.0.

SPECT imaging and analysis

All participants underwent SPECT twice—before pharmacologic treatment (baseline assessment) and at the time of the second HRSD evaluation (approximately 13.7 weeks after the baseline assessment). CBF imaging of participants was performed by SPECT using ethyl-cisteinate-dimer labeled with technetium-99m (^{99m}Tc-ECD) as a radiotracer. The images were obtained after an intravenous bolus injection of approximately 600 MBq of ^{99m}Tc-ECD using a multi-detector scanner (ECAM Plus; Siemens, Erlangen, Germany). Statistical analysis was performed using the SPM99 software (Wellcome Trust Centre for Neuroimaging, London, UK) on the MATLAB (The Mathworks, Inc., Natick, MA, USA). The SPM program was used to perform a paired *t*-test on a voxel-by-voxel basis to identify the profile of voxels that differed significantly between two images. The images were transformed and then normalized to the SPM-SPECT template, which is based on the Montreal Neurological Institute (MNI) standard anatomical space. Standardized images were then smoothed with a full-width-at-half-maximum of 8 mm. The activation maps were generated by applying both the clustering threshold and *t*-threshold corresponding to a statistical level of $p < 0.01$.

The initial baseline SPECT data were compared with 20 age-matched healthy controls (age range, 61–70 years) drawn from a larger database from the National Center Hospital for Mental, Nervous, and Muscular Disorders using paired *t*-tests. Resulting statistics were transformed to *z*-scores and presented graphically in the Talairach-Tournoux coordinate system (Talairach and Tournoux, 1988). Each participant's SPECT data at the second assessment was compared with data from baseline using paired *t*-tests.

RESULTS

Figure 1 shows the areas of hypoperfusion of patients compared with healthy controls ($p < 0.01$). Patients with depression demonstrated decreased rCBF in the anterior ventral and dorsal medial PFC including the ACC, bilateral ventrolateral PFC to temporal cortices, and bilateral medial to lateral parieto-occipital lobes relative to healthy control subjects. No particular areas showed increased rCBF compared with healthy controls. There were no significant correlations between symptom severity as indexed by HRSD and rCBF in particular areas.

Figure 2 shows the areas in which rCBF significantly increased after pharmacotherapy compared with baseline in individuals with depression ($p < 0.01$). Areas showing recovered rCBF in the follow-up SPECT were distributed most prominently in the left dorsolateral PFC to the precentral areas and the right parieto-occipital regions. However, decreased rCBF at baseline in the anterior ventral/dorsal medial PFC, bilateral ventrolateral PFC, bilateral temporal lobes

DOI: 10.1002/gps

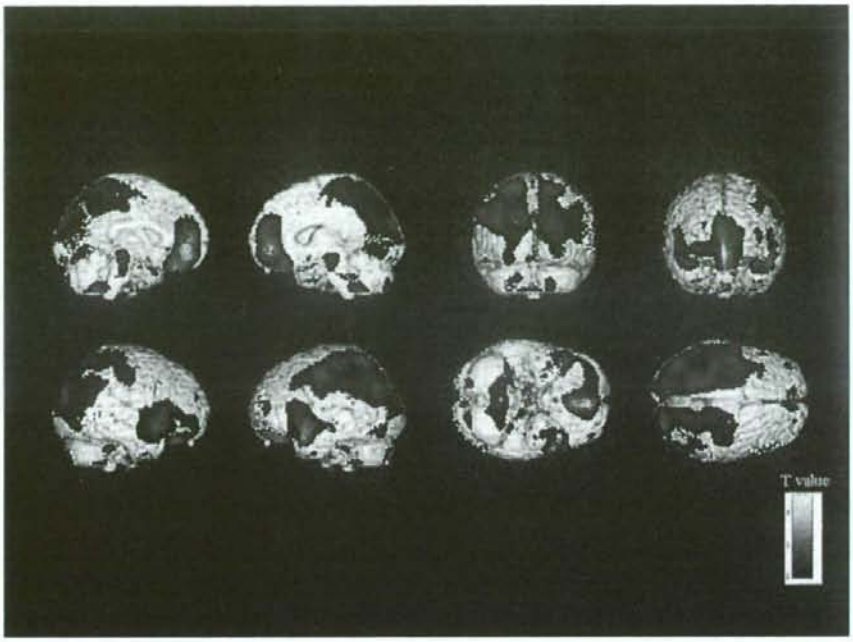

Figure 1. The brain images show the areas of hypoperfusion of patients compared with healthy controls ($p < 0.01$). Patients with depression demonstrated decreased rCBF in the anterior ventral and dorsal medial PFC including the ACC, bilateral ventrolateral PFC to temporal cortices, and bilateral medial to lateral parieto-occipital lobes relative to healthy control subjects.

and bilateral parietal lobes did not show significant improvement even after treatment.

DISCUSSION

In our study, compared with healthy elderly controls, individuals with late-life depression demonstrated decreased rCBF in the anterior ventral and dorsal medial PFC including the ACC, bilateral ventrolateral PFC to temporal cortices, and bilateral medial to lateral parieto-occipital lobes. The results partially support the notion of hypofrontality in patients with late-life depression as shown by most previous functional neuroimaging research (Upadhyaya *et al.*, 1990; Curran *et al.*, 1993; Philpot *et al.*, 1993; Ebmeier *et al.*, 1998; Navarro *et al.*, 2001). Specifically, our results are consistent with those of Navarro *et al.* (2001) in that rCBF of patients with unmedicated late-onset unipolar major depression showed significant decreases in both the left and right anterior frontal regions. Although rCBF decreases in the anterior frontal regions by Navarro *et al.* (2001) were more pronounced in the left hemisphere, no reliable right-left perfusion differences were noted in the present study.

The present study demonstrated significant hypoperfusion in the posterior brain regions bilaterally, which were in accordance with previous findings (Shlegel *et al.*, 1989; Austin *et al.*, 1992). Of note, however, Ebmeimer *et al.* (1998) claimed that rCBF in the parietal lobes is well preserved in late-life depression, and this finding of lack of parietal hypoperfusion may contribute to differentiating late-life depression from Alzheimer's disease. Bonne *et al.* (2003) suggested a possible heterogeneity of imaging techniques and data-analytic procedures in interpreting the results of SPECT. Their patients with depression demonstrated decreased rCBF in the right parietal and occipital lobes by both region of interest (ROI) and SPM analyses, but additional regions were identified only on ROI analysis (left temporal) or only on SPM analysis (left parietal). Caution should be paid to the methodological differences while interpreting the perfusion results.

We examined whether the decreased rCBF in individuals with late-life depression may resolve

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