Altered expression of BDNF, BDNF pro-peptide and their precursor proBDNF in brain and liver tissues from psychiatric disorders: rethinking the brain–liver axis

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INTRODUCTION

Multiple lines of evidence suggest that brain-derived neurotrophic factor (BDNF) is crucial in the pathophysiology of psychiatric disorders, such as major depressive disorder (MDD), schizophrenia (SZ) and bipolar disorder (BD).1–6 Brain-derived neurotrophic factor (mature form) is a 13 kDa polypeptide, which is initially synthesized as the precursor protein, proBDNF, in the endoplasmic reticulum. Following cleavage of the signal peptide, proBDNF (~32 kDa) is converted to mature BDNF and BDNF pro-peptide (~17 kDa), the N-terminal fragment of proBDNF (Figure 1). Both proBDNF and mature BDNF are active, eliciting opposing effects via the p75NTR and tropomyosin-related kinase B (TrkB) receptor, respectively, and both forms are important in several physiological functions.7–11 The expression levels of BDNF pro-peptide are increased during postnatal development and plateau in adult mice. In addition, BDNF pro-peptide is released from neurons in an activity-dependent manner.12 Interestingly, BDNF pro-peptide directly facilitates hippocampal long-term depression, requiring activation of the GluN2B subtype of N-methyl-D-aspartate receptors and p75NTR.13 A recent study showed that neuronal depolarization elicited a marked increase in extracellular BDNF pro-peptide, which, in turn, negatively regulated dendritic spines via caspase-3.14 Taken together, it is likely that proBDNF, BDNF pro-peptide and mature BDNF all share important biological functions.

Increased levels of BDNF protein in the anterior cingulate cortex and hippocampus of patients with SZ have been reported.15,16 However, Weickert et al.17 reported a significant reduction in BDNF messenger RNA (mRNA; 23%) and BDNF protein (40%) in the dorsolateral prefrontal cortex of SZ patients. Issag et al.18 also reported decreased BDNF in the prefrontal cortex of SZ patients. Moreover, the levels of proBDNF and BDNF pro-peptide in the cerebellum of MDD, SZ and BD groups were significantly lower than controls. In contrast, the levels of proBDNF and BDNF pro-peptide in the cerebellum of MDD, SZ and BD groups were significantly higher than the control group. The levels of mature BDNF in the spleen did not differ among the four groups. Interestingly, there was a negative correlation between mature BDNF in the parietal cortex and mature BDNF in the liver in all the subjects. These findings suggest that abnormalities in the production of mature BDNF and BDNF pro-peptide in the brain and liver might have a role in the pathophysiology of psychiatric disorders, indicating a brain–liver axis in psychiatric disorders.
cerebellum, liver and spleen) taken from SZ, MDD and BD groups showed differences when compared with a healthy control group.

**MATERIALS AND METHODS**

**Postmortem human samples**

Human postmortem parietal cortex (Brodmann area 7), cerebellum, liver and spleen from normal controls (N=15), as well as patients with MDD (N=15), SZ (N=15) and BD (N=15) were obtained from the Stanley Foundation Brain Collection (Bethesda, MD, USA). The spleen samples from three SZ patients and one MDD patient were not included. The specimens are collected by medical examiners. Permission from the next of kin was obtained in all the cases. The demographic, clinical and storage information for cases has been previously published. Each diagnostic group was matched according to several parameters, including age at death, gender, postmortem interval, brain pH and brain weight (Table 1). This study was approved by the Research Ethics Committee of the Graduate School of Medicine, Chiba University (No. 442 on 16 September 2015 and No. 223 on 13 June 13 2016).

**Western blot analysis**

The western blot analysis was performed by one observer who was blinded to the four groups. Human samples were stored at −80 °C until biochemical analyses. The tissue samples were homogenized in Laemmlili lysis buffer, then centrifuged at 3000 g at 4 °C, for 10 min to obtain the supernatants. The protein concentrations were determined using a BCA method assay kit (Bio-Rad, Hercules, CA, USA), then the samples were incubated for 5 min at 95 °C, with an equal volume of 125 mM Tris/HCl, pH 6.8, 20% glycerol, 0.1% bromophenol blue, 10% β-mercaptoethanol and 4% sodium dodecyl sulfate. The proteins were separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, on 10% mini-gels (Mini-PROTEAN TGX Precast Gel; Bio-Rad). The separated proteins were then transferred onto polyvinylidene difluoride membranes using a Trans Blot Mini Cell (Bio-Rad). For immunodetection, the blots were blocked with 2% BSA in TBST (TBS+0.1% Tween-20) for 1 h at room temperature, then incubated with primary antibodies overnight, at 4 °C. The following primary antibodies were used: anti-human proBDNF (1:2000, Cat #: H10001G-MA, GeneCopoeia, Rockville, MD, USA), anti-BDNF (1:200, Cat #: H-117 (sc-20981), Santa Cruz Biotechnology, Santa Cruz, CA, USA) and β-actin (1:10 000, Sigma-Aldrich, St Louis, MO, USA). Anti-human proBDNF antibody (GeneCopoeia) and anti-BDNF (Santa Cruz Biotechnology) were used for the measurement of proBDNF, BDNF pro-peptide and mature BDNF, respectively. The specificity of these BDNF antibodies was confirmed using brain samples from 8dnf knockout rats. The next day, the blots were washed three times in TBST and incubated with horseradish peroxidase conjugated anti-rabbit or anti-mouse antibody (1:2000). The bands were visualized using enhanced chemiluminescence, plus the western blotting detection system (GE Healthcare Bioscience, Tokyo, Japan). The images were captured with a Fuji LAS3000–film, Tokyo, Japan), and immunoreactive bands were quantified.

**Statistical analysis**

The data were shown as the mean ± s.d. The analysis was performed using PASW Statistics 20 (formerly SPSS statistics; SPSS, Tokyo, Japan). Analyses were performed using one-way analysis of variance (ANOVA). The data are shown as the mean ± s.d.

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**Figure 1.** Production of BDNF and BDNF pro-peptide from its precursor. The human BDNF gene produces proBDNF protein, which is processed to proBDNF (~32 kDa). Following cleavage of the signal peptide, proBDNF (~32 kDa) is converted to BDNF mature form (~13 kDa) and BDNF pro-peptide (~17 kDa) by intracellular and extracellular proteases. Mature BDNF preferentially binds the TrkB receptor, while proBDNF and BDNF pro-peptide bind to p75NTR. BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase B.

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**Table 1.** Characteristics of the postmortem samples from Neuropathology Consortium of the Stanley Medical Research Institute

| Characteristics                  | Control (n=15)     | MDD (n=15)     | SZ (n=15)    | BD (n=15)    | P-value |
|----------------------------------|--------------------|----------------|--------------|--------------|---------|
| Age at death (years)             | 48.1 ± 10.7        | 46.5 ± 9.3     | 44.5 ± 13.1  | 42.3 ± 11.7  | 0.540†  |
| (29–68)                          | (30–65)            | (25–62)        | (25–61)      |              |         |
| Gender (male/female)             | 9/6                | 9/6            | 9/6          | 9/6          |         |
| (PMI (h))                        | 23.7 ± 9.95        | 27.5 ± 10.7    | 33.7 ± 14.6  | 32.5 ± 16.1  | 0.147†  |
| (9/6)                            |                    | (32.2 ± 16.1)  |              |              |         |
| Brain pH                         | 6.27 ± 0.24        | 6.18 ± 0.21    | 6.16 ± 0.26  | 6.18 ± 0.23  | 0.616†  |
| (6/9)                            |                    | (6/9)          | (6/9)        | (8/7)        |         |
| Brain hemispheres (right/left)   | 7/8                | 6/9            | 6/9          | 8/7          | 0.864†  |
| Brain weight (g)                 | 1501.0 ± 164.1     | 1462.0 ± 142.1 | 1471.7 ± 108.2 | 1441.2 ± 171.5 | 0.740†  |
| Storage days                     | 3382.3 ± 234.2     | 4340.0 ± 290.0 | 621.1 ± 233.1 | 620.5 ± 172.3 | 0.003‡  |
| (4 without)                      |                    | (21.5 ± 8.4)   | (21.5 ± 8.4) | (20.1 ± 9.7) |         |
| (15)                             |                    | (11 with)      | (11 with)    | (11 with)    |         |
| Fluphenazine equivalent (mg)     | 52267 ± 62062      | 20827 ± 24016  |              |              | 0.084d  |
| (1 never)                        |                    | (1 never)      |              |              |         |

Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; PMI, postmortem interval; SZ, schizophrenia. †One-way analysis of variance. ‡χ² test for independence. †Fisher’s exact probability test. dUnpaired t-test. The data are shown as the mean ± s.d.
of covariance (ANCOVAs) were performed on normalized spot volumes, for each spot in each region, with brain pH, age of disease onset, gender, duration of disease, postmortem interval, frozen brain hemisphere side, lifetime neuroleptic drug use, severity of substance abuse, severity of alcohol abuse and/or frozen storage time. If ANCOVA reached significance, we performed the post hoc least significance difference test to identify group comparisons. Correlation was determined by Pearson or nonparametric Spearman correlations. A P-value $< 0.05$ was considered to be statistically significant.

RESULTS

As the postmortem samples have many parameters, the ANCOVA has been used for statistical analyses of the data. The ANCOVA of the data from the parietal cortex showed the statistical results; [proBDNF: $F_{3,56} = 0.500, P = 0.684$], [BDNF pro-peptide: $F_{3,56} = 4.400, P = 0.008$], [mature BDNF: $F_{3,56} = 6.087, P = 0.001$] from the four groups. A post hoc analysis showed that expression of BDNF pro-peptide in MDD ($P = 0.005$), SZ ($P = 0.001$) and BD ($P = 0.002$) groups was significantly higher than in the control group (Figure 2). In contrast, expression of mature BDNF in the MDD ($P = 0.001$), SZ ($P < 0.001$) and BD ($P = 0.002$) groups was significantly lower than in the control group (Figure 2).

Furthermore, the ANCOVA of the data from the cerebellum showed the statistical results; [proBDNF: $F_{3,56} = 5.603, P = 0.002$], [BDNF pro-peptide: $F_{3,56} = 3.044, P = 0.039$], [mature BDNF: $F_{3,56} = 0.275, P = 0.843$] among the four groups. A post hoc analysis
showed that expression of proBDNF, and BDNF pro-peptide in the MDD (proBDNF: $P_{\text{BDNF}} = 0.001$, BDNF pro-peptide: $P_{\text{BDNF}} = 0.015$), SZ (proBDNF: $P_{\text{BDNF}} = 0.001$, BDNF pro-peptide: $P_{\text{BDNF}} = 0.011$) and BD (proBDNF: $P_{\text{BDNF}} = 0.002$, BDNF pro-peptide: $P_{\text{BDNF}} = 0.019$) groups was significantly lower than in the control group (Figure 2).

Moreover, the ANCOVA of the data from the liver showed the statistical results; [proBDNF: $F_{3,56} = 1.594$, $P_{\text{BDNF}} = 0.202$], [BDNF pro-peptide: $F_{3,56} = 0.039$, $P_{\text{BDNF}} = 0.990$], [mature BDNF: $F_{3,56} = 3.010$, $P_{\text{BDNF}} = 0.044$] among the four groups. A post hoc analysis showed that expression of mature BDNF in the MDD ($P_{\text{BDNF}} = 0.021$), SZ ($P_{\text{BDNF}} = 0.016$) and BD ($P_{\text{BDNF}} = 0.023$) groups was significantly lower than in the control group (Figure 3). The ANCOVA of the data from the spleen showed the statistical results; [proBDNF: $F_{3,52} = 4.369$, $P_{\text{BDNF}} = 0.009$], [BDNF pro-peptide: $F_{3,52} = 3.352$, $P_{\text{BDNF}} = 0.034$], [mature BDNF: $F_{3,52} = 0.085$, $P_{\text{BDNF}} = 0.968$] among the four groups. A post hoc analysis showed that the expressions of mature BDNF and BDNF pro-peptide in the MDD (proBDNF: $P_{\text{BDNF}} = 0.003$, BDNF pro-peptide: $P_{\text{BDNF}} = 0.008$) and BD (proBDNF: $P_{\text{BDNF}} = 0.004$, BDNF pro-peptide: $P_{\text{BDNF}} = 0.021$) groups were significantly lower than those of the control group (Figure 3).

We analyzed the correlation between protein expression in the brain and liver. Interestingly, we found a negative correlation ($r = -0.270$, $P = 0.037$) between mature BDNF in the liver and mature BDNF in the parietal cortex in all the subjects (Figure 4a).
Furthermore, there was a positive correlation ($r = 0.288$, $P = 0.026$) between proBDNF in the cerebellum and proBDNF in the liver in all the subjects ($N = 60$). BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; SZ, schizophrenia.

Next, we analyzed the correlation between protein expression in the brain and spleen. There was a negative correlation ($r = -0.266$, $P = 0.048$) between BDNF pro-peptide in the parietal cortex and BDNF pro-peptide in the spleen in all the subjects (Figure 5a). Furthermore, there was also a positive correlation ($r = 0.387$, $P = 0.003$) between BDNF pro-peptide in the cerebellum and BDNF pro-peptide in the spleen in all the subjects ($N = 56$). BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; SZ, schizophrenia.

DISCUSSION

The major findings of this study are as follows: First, tissue levels of mature BDNF in the parietal cortex from MDD, SZ and BD groups were significantly lower than those of the control group. Interestingly, the tissue levels of BDNF pro-peptide in the parietal cortex from MDD, SZ and BD groups were significantly higher than in the control group. Second, the tissue levels of proBDNF and BDNF pro-peptide in the cerebellum from MDD, SZ and BD groups were significantly lower than those of the control group. Third, the tissue levels of mature BDNF in the liver from MDD, SZ and BD groups were significantly lower than controls. Fourth, the tissue levels of proBDNF and BDNF pro-peptide in the spleen from MDD, SZ and BD groups were significantly lower than in controls. Finally, there were correlations between BDNF isoforms in the brain and liver (or spleen) in all the subjects. Taken together, it is likely that abnormalities in the production of mature BDNF and BDNF pro-peptide from their precursor proBDNF in the brain and peripheral tissues may have a role in the pathophysiology of major psychiatric disorders.

The parietal cortex, one of four major lobes in the cerebral cortex of the human brain, has important roles in integrating sensory information from various parts of the body. In this study, we found decreased expression of mature BDNF and increased expression of BDNF pro-peptide in parietal cortices from the three major psychiatric disorders. It is therefore likely that decreased BDNF–TrkB signaling and increased BDNF pro-peptide–p75NTR signaling in the parietal cortex is crucial to the pathophysiology of these psychiatric disorders. Previous reports using western blot analysis showed reduced BDNF protein expression in the dorsolateral prefrontal cortex of SZ patients. A study using BDNF enzyme-linked immunosorbent assay (ELISA; Promega, Tokyo, Japan) kits showed increased BDNF in many brain regions, including parietal cortex from SZ compared with control groups. As this ELISA kit recognizes both mature and precursor proBDNF due to the limited specificity of its BDNF antibody, the obtained data represent total levels of mature BDNF and its precursors.

Accumulating evidence suggests that the cerebellum is vital to many motor, cognitive and emotional processes, despite earlier
beliefs that its role was limited to motor coordination. In this study, we found decreased expression of proBDNF and BDNF pro-peptide in the cerebella of psychiatric disorder patients. Thus, it is likely that decreased proBDNF (or BDNF pro-peptide)–p75NTR signaling in the cerebellum may mediate the pathological processes underlying psychiatric disorders, although further investigations are needed. The reasons underlying the opposing findings in the parietal cortex and cerebellum are currently unknown.

A large-scale retrospective study reported a higher prevalence of liver disease and alcohol-related cirrhosis in veterans with SZ or BD. A subsequent population-based cohort study found that SZ and BD patients showed a significantly higher prevalence and incidence of chronic liver disease than the general population, and that even younger patients had a much higher prevalence and incidence of liver disorders than the general population. Thus, there is a possible link between liver disease and SZ and BD. Furthermore, the high expression of BDNF and TrkB proteins in liver suggests neurotrophic support for autonomic innervation of this organ. It is reported that BDNF can normalize liver weights and the glycogen content of db/db mutant mice, and that these changes were not entirely associated with reduced food intake. Teillon et al. demonstrated that BDNF–TrkB signaling facilitated the development of metabolic disorders and liver damage, elicited by a high-fat diet. In contrast to the appetite-inhibiting effects of BDNF on the brain, it seems that BDNF in the liver might promote the detrimental effects of dietary stress, highlighting the complexity of BDNF signaling in these two organs. We found increased levels of mature BDNF in livers from the three psychiatric disorders. Interestingly, we found a negative correlation between mature BDNF in the parietal cortex and mature BDNF in the liver, suggesting a role of brain–liver axis. Given the postulated role for the brain–liver axis, it is likely that increased levels of mature BDNF in liver tissue might contribute to the high incidence of liver disease in these psychiatric disorders. Nonetheless, further detailed studies of the underlying association between BDNF–TrkB signaling in the brain–liver axis and psychiatric disorders are needed.

It is reported that high-fat diet (21 weeks) caused a decrease in the BDNF (mature form) in the mouse brain (prefrontal cortex, hippocampus) as well as liver, suggesting that high-fat diet-induced reduction of BDNF–TrkB signaling in these tissues may have a role in the insulin resistance and the development of hepatic steatosis in mice. As the dietary details of the control are not available, the role of dietary effects on BDNF isoforms in these tissues is unknown. Nonetheless, further study on role of diet on BDNF isoforms in the brain and peripheral tissues is needed.

Yamamoto et al. reported high expression of BDNF mRNA and low levels of TrkB mRNA in human spleen. A previous report showed that congenital absence of the thymus results in congenital absence of the thymus and BD patients showed a significantly higher prevalence and incidence of liver disorders than the general population. Thus, there is a possible link between liver disease and BD in clinical practice. Recent studies using blood samples suggest that the measurement of mature BDNF and proBDNF in blood would be potential diagnostic biomarkers for MDD and BD. Therefore, the measurement of three BDNF isoforms (proBDNF, mature BDNF, BDNF pro-peptide) in the blood will be of great interest for potential diagnostic biomarkers for MDD and BD.

In conclusion, this study suggests that abnormal metabolism of proBDNF into mature BDNF and BDNF pro-peptide in the brain and liver may be crucial to the development of psychiatric disorders. Further detailed investigations into this association between the brain–liver axis and psychiatric disorders are warranted.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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