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Significantly decreased mRNA levels of *BDNF* and *MEK1* genes in treatment-resistant depression

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Abstract

The aim of the current study was to investigate whether the levels of mRNA expression of brain-derived neurotrophin factor (BDNF) and a related gene *MEK1* were more obviously decreased in treatment-resistant depression (TRD). In total, 50 patients with major depressive disorder (including 26 with TRD and 24 with treatment-responsive depression) and 48 healthy controls were enrolled. BDNF and MEK1 mRNA levels in blood samples from all patients and controls were measured using reverse transcriptase-PCR. BDNF and MEK1 mRNA levels were significantly reduced in patients with major depressive disorder when compared with healthy controls (BDNF: $P<0.01$; MEK1: $P<0.001$), as well as among treatment-resistant depressive patients as compared with treatment-responsive depressive patients (BDNF: $P<0.001$; MEK1: $P<0.01$). Our findings support the hypothesis that BDNF and MEK1 mRNA expression levels are more obviously decreased in patients with TRD.

Keywords

brain-derived neurotrophin factor; mitogen-activated protein kinase kinase 1; treatment-resistant depression; treatment-responsive depression

Introduction

Despite significant progress in the development of antidepressants, ~40% of patients with major depressive disorder (MDD) still only show partial or no response to either initial or

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multiple antidepressant treatments, a phenomenon commonly known as treatment-resistant depression (TRD) [1]. TRD was estimated to be the main contributing factor toward the economic burdens of depression [2]. Accordingly, there have been significant efforts toward identification of markers that predict antidepressant treatment response or risk. However, despite considerable research efforts, the mechanisms that underlie TRD are still poorly understood.

The 'neurotrophin hypothesis' posits that central BDNF deficiencies underlie MDD, and that antidepressants work through restoration of central BDNFactivities [3–6]. This is not an unreasonable assumption, as among MDD patients both the central and the peripheral levels of BDNF are often decreased and can potentially be upregulated through antidepressant treatment [6–9].

Alongside BDNF, mitogen-activated protein kinase kinase 1/2 (also known as MEK1/2), which is an immediate activator of the MEK–ERK pathway mediated by BDNF, is also found to be decreased in depressive patients and can be upregulated by administration of antidepressants [10].

Succinctly, previous studies found that BDNF and MEK1 are involved in the pathogenesis of depressive disorder and mechanisms of antidepressant treatment. However, whether BDNF and MEK1 are also involved in the pathogenesis of TRD is unclear, as is whether mRNA levels of BDNF and MEK1 in peripheral blood mono-nuclear cells are more obviously decreased in patients with TRD. In this study, we accordingly hypothesized that levels of mRNA expression of BDNF and MEK1 are decreased in MDD patients and obviously decreased in patients with TRD.

Methods

Patient recruitment

In total, 50 patients diagnosed with MDD according to the *Diagnostic and Statistical Manual of Mental Disorders* – 4th ed. criteria, as well as 48 age-matched and sex-matched healthy controls, who were employees or students of the Mental Health Center at Shanghai Jiao Tong University, were included in this study. Patients were rated on the basis of the 24-item Hamilton Depression Rating Scale (HAMD-24). The total scores of HAMD-24 for all patients exceeded 20. According to the previous treatment outcomes, the 50 MDD patients included 26 patients with TRD and 24 patients with treatment-responsive depression (TSD). Patients in whom treatment with two or more antidepressants from different classes with adequate treatment durations and dosages failed were considered to have TRD [1,11]. Patients who responded to treatment with at least one antidepressant were considered to have TSD. Peripheral blood was also collected from controls who were vetted as being physically healthy, without a history of psychiatric or serious somatic disease.

All procedures were reviewed and approved by the ethical committee of Shanghai Mental Health Center. Written informed consent was obtained from each participant before any study-related procedure was performed.

Quantitative real-time PCR

To study mRNA expression, RNA was extracted from the peripheral leukocytes of whole blood samples using the QIAamp RNA Blood Mini Kit (Qiagen, Chatsworth, California, USA) and treated with DNase (Qiagen) in tubes. Next, cDNA was synthesized using Omniscript reverse transcription reagents (Qiagen) with random primers. The samples were stored at −70°C for further use. Real-time quantitative reverse transcriptase-PCR was performed in triplicate for each sample on an ABI Prism 7900HT Sequence Detection System with TaqMan Universal PCR MasterMix (Applied Biosystems, Foster City, California, USA) according to the manufacturer's protocol. Assays, which are probe/primer sets specific to *BDNF* (Hs00156058_m1), *MEK1* (Hs00605615_mH), and the housekeeping control gene (glyceraldehyde-3-phosphate dehydrogenase) probe (Hs99999905_ml), were purchased from Applied Biosystems. Analysis of relative gene expression was carried out using the $2^{-\Delta\Delta C_t}$ method, and data were normalized to glyceraldehyde-3-phosphate dehydrogenase expression [12].

Statistical analysis

Statistical calculations were carried out using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to assess the normality of mRNA expression levels. When the data were not normally distributed, nonparametric tests were performed. Differences in gene expression level between the different groups were assessed using the Mann–Whitney *U*-test.

The relationships between gene expression levels and depression severity score (HAMD-24) were assessed using Spearman's rank correlation coefficient. All significance levels were two-sided, with *P* less than 0.05 being considered statistically significant.

Results

In total, 50 MDD patients (24 male and 26 female; 26 TRD patients and 24 TSD patients), and 48 age-matched and sex-matched healthy controls (23 male and 25 female) were included in this study. There is no significant difference in the HAMD total scores between TRD and TSD patients (t= 0.789, P> 0.05). Analysis showed that the mRNA levels of BDNF and MEK1 were non-normally distributed according to the Kolmogorov–Smirnov test (BDNF: P< 0.001; MEK1: P < 0.05). mRNA levels of BDNF and MEK1 were significantly reduced in patients with MDD as compared with healthy controls (BDNF: P < 0.01; MEK1: P < 0.001; shown in Table 1). mRNA levels of BDNF and MEK1 were significantly lower among TRD patients as compared with TSD patients (BDNF: P < 0.001; MEK1: P < 0.01; shown in Table 1). However, no significant correlations were found between the mRNA levels of BDNF and MEK1 and the total HAMD-24 scale scores (BDNF: r = − 0.189, P > 0.05; MEK1: r= − 0.269, P > 0.05).

Discussion

The main findings of the present study were that the mRNA levels of BDNF and MEK1 were significantly decreased in patients with MDD as compared with healthy controls.

Among the patients with MDD, the mRNA levels of BDNF and MEK1 were significantly reduced in TRD patients as compared with TSD patients.

As mentioned earlier, the ‘neurotrophic hypothesis’ suggests that dysfunction of neural networks is involved in the pathogenesis of MDD and the mechanisms of action of antidepressants [13–15]. Neurotrophic factors play critical roles in the plasticity of neural networks. Previous animal models and postmortem studies have found that BDNF expression levels are decreased in some brain areas [6,16,17]. Likewise, BDNF expression levels were significantly decreased in peripheral blood of patients with MDD, including BDNF mRNA levels in lymphocytes and BDNF levels in serum and plasma [18,19]. In the current study, mRNA levels of BDNF and MEK1 were significantly reduced in patients with MDD as compared with healthy controls ($P < 0.05$). Consequently, these observations are consistent with those of most prior studies, bolstering the notion that downregulation of BDNF and MEK1 may be involved in the pathogenesis of MDD.

Interestingly, we found that mRNA levels of BDNF and MEK1 were significantly lower in TRD patients when compared with TSD patients. In this study, there is no difference in HAMD scores between TRD and TSD patients. Therefore, the difference in mRNA levels of BDNF and MEK1 between TRD and TSD patients is not attributed to the severity of depressive symptoms. Accordingly, our finding potentially indicates more severe neurotrophic dysfunction in TRD patients. Our finding also triggers further hypotheses that medications that can improve neural plasticity may become the new choice for treatment of TRD, and levels of BDNF and MEK1 can be used as biomarkers of treatment response.

Although interesting, there are several limitations to this study that should be noted. First, these findings should be considered preliminary, on the basis of a sample size of 50 patients. Second, there are several factors that indicate neurotrophy and neural plasticity. Third, considering the safety of patients and ethics, there was no requirement for a wash-out period in this study. In this study, both TRD and TSD patients had been administering antidepressants before participation in this study. However, all patients were in the period of depressive onset with more than 20 points on the HAMD-24 scale and did not receive new treatment before blood collection. Future studies with larger samples, more factors, and more strict inclusion criteria will help verify the findings of this study.

In summary, we detected significantly reduced BDNF and MEK1 mRNA levels in patients with MDD, especially patients with TRD. The findings of this study support the neurotrophic hypothesis of depression and indicate more severe neurotrophic dysfunction in TRD patients.

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Table 1

Demographics, depression ratings, and medians of the relative mRNA expression levels of BDNF and MEK1 of study participants

	Controls	MDD	TRD	TSD
N	48	50	26	24
Age	39.4±12.5	44.6±13.3	43.9±12.5	45.4±14.3
Sex (Female)	25	26	10	16
HAMD-24	–	35.41 ±9.74	36.45±9.84	33.87±9.72
Level of BDNF [median (25th, 75th)]	2.73 (1.41, 15.47)	1.72 (0.64, 4.10)$**	0.79 (0.32, 1.63)	3.85 (1.93, 6.34)&***
Level of MEK1 [median (25th, 75th)]	5.63 (4.13, 7.58)	0.74 (0.44, 2.64)$***	0.60 (0.41, 1.97)	1.17 (0.61, 3.40)&**

BDNF, brain-derived neurotrophin factor; HAMD-24, 24-item Hamilton Depression Rating Scale; MDD, major depressive disorder; TRD, treatment-resistant depression; TSD, treatment-responsive depression.

$** Different from ‘health control’, $P < 0.01$.

$*** Different from ‘health control’, $P < 0.001$.

&** Different from ‘TRD’, $P < 0.01$.

&*** Different from ‘TRD’, $P < 0.001$.