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LETTER TO THE EDITOR

Epigenetic regulation of BDNF expression according to antidepressant response

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Several lines of evidence support the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology and pharmacotherapy of depression.[1] The neurotrophin hypothesis of depression postulates that stress and depression are associated with decreased BDNF expression, which can be reversed by antidepressant treatment.[2] The goal of the present study was to investigate the effect of antidepressant treatment on the epigenetic regulation of BDNF in major depressive disorder (MDD).

The *BDNF* gene has distinct splice variants, each regulated by a specific promoter region, that determine tissue-specific regulation of expression.[3] Of these variants, BDNF-IV is the most commonly studied, and its expression changes have been associated with behavioral phenotypes, psychiatric disorders and epigenetic modifications.[4] The promoter region in exon-IV contains specific binding sites for the cyclic-AMP-responsive-element-binding protein[5] and the methyl-CpG-binding-protein-2,[6] making it a preferential candidate for epigenetic regulation.

Tsankova *et al.*[7] reported that mice exposed to chronic social defeat stress displayed lower levels of BDNF-IV associated with a significant increase in histone H3 lysine 27 trimethylation (H3K27me3), a modification associated with transcriptional repression. Long-term imipramine treatment reversed BDNF-IV down-regulation to baseline levels.[7] Studies by our group in the postmortem brain of depressed subjects with or without history of antidepressant treatment compared with controls showed an increased expression of BDNF-IV and a decrease of H3K27 trimethylation levels in subjects treated with antidepressants only.[8]

In order to investigate the epigenetic regulation of BDNF in MDD patients according to antidepressant treatment, we conducted a prospective study in 25 treatment-naive MDD patients. All patients had Hamilton Rating Scale for Depression (HAM-D) scores $\geqslant 24$ at baseline ($N = 25$, $X = 29.4 \pm 1.2$). All participants gave written informed consent for this study, which was approved by our Institutional Review Board.

Subjects were excluded from the study if they had comorbidity with other major psychiatric disorders, if they had positive tests for illicit drugs at any point during the study or if they had general medical illnesses. Patients (12 males and 13 females) were treated with citalopram, starting with an initial dose of 10 mg die, which was titrated progressively to a maximum of 60 mg die. All final doses were within the therapeutic range and blood levels of total BDNF and H3K27me3 were measured at baseline (T0) and after 8 weeks (T8) of treatment. Subject treatment compliance was assessed using high-performance liquid chromatography at the end of the trial. All subjects showed detectable plasma citalopram levels and we observed a significant correlation between citalopram dose and plasma concentration (Spearman's $r = 0.54$; $P = 0.005$).

A repeated-measures ANOVA with Bonferroni correction revealed that in line with previous findings, the expression of peripheral BDNF mRNA in depressed patients ($N = 25$) was significantly elevated after 8 weeks of citalopram treatment (FC = 34%; $P < 0.001$; Figure 1a). Subjects were classified into responders (RES) and non-responders (NRES), based on changes to the HAM-D scores. We defined response as 8-week HAM-D scores < 9, whereas non-response was defined as 8-week HAM-D scores $> 50\%$ reduction in baseline HAM-D scores (T8; RES = 5.6 ± 0.7; $N = 15$; NRES = 17.0 ± 1.4; $N = 10$). The RES group showed increased BDNF levels (T8–T0; FC = 49%; $P < 0.001$; Figure 1a) after treatment, whereas there was no significant difference in the NRES group (T8–T0; FC = 3%; $P > 0.05$; Figure 1a). Consistently, RES had higher T8 BDNF levels as compared with NRES (*T*-test $P < 0.05$; Figure 1c), whereas there was no difference at T0 (*T*-test $P = 0.98$; Figure 1c). Finally, we found a significant correlation between change in depression severity and change in BDNF expression (Pearson's $r = 0.49$; $R^2 = 0.25$; $P < 0.05$; Figure 1f). These findings indicated a relationship between peripheral BDNF expression and citalopram treatment response.

To investigate the role of chromatin modifications in BDNF expression changes, based on previous findings in rodents,[7] we performed chromatin immunoprecipitation (ChIP) and found a significant decrease in H3K27me3 levels at promoter-IV of the BDNF gene after 8 weeks of citalopram treatment in all patients ($N = 25$) according to a repeated-measures ANOVA with Bonferroni correction (FC = 31%; $P < 0.001$; Figure 1b). However, these results were explained primarily by changes in the RES group (FC = 43%; $P < 0.001$; Figure 1b), and there was no significant difference in the NRES group ($P > 0.05$; Figure 1b). Consistently, we found a significant difference in H3K27me3 levels at T8 between groups (*T*-test $P < 0.01$; Figure 1d), but no difference at T0 (*T*-test $P > 0.05$; Figure 1d). Furthermore, we found a significant negative correlation between change in depression severity and change in H3K27me3 expression (Pearson's $r = -0.63$; $R^2 = 0.39$; $P < 0.01$; Figure 1g). Finally, total BDNF and H3K27me3 levels were significantly negatively correlated (Pearson's $r = -0.86$; $R^2 = 0.75$; $P < 0.0001$; Figure 1e).

To our knowledge, this is the first study that translates to human findings previously reported in an animal model of depression,[7] reporting evidence suggesting that antidepressants regulate BDNF expression through alterations of promoter-IV H3K27me3 levels. Our results suggest that changes in H3K27 methylation state of the BDNF promoter IV and BDNF expression levels in peripheral tissue are biomarker correlates of antidepressant response. Finally, these findings are preliminary and await confirmation by larger samples and alternative designs. Moreover, additional work is necessary to better understand the relationship between epigenetic modifications and the exon-specific regulation of BDNF, as this has the potential to lead to new therapeutic options for MDD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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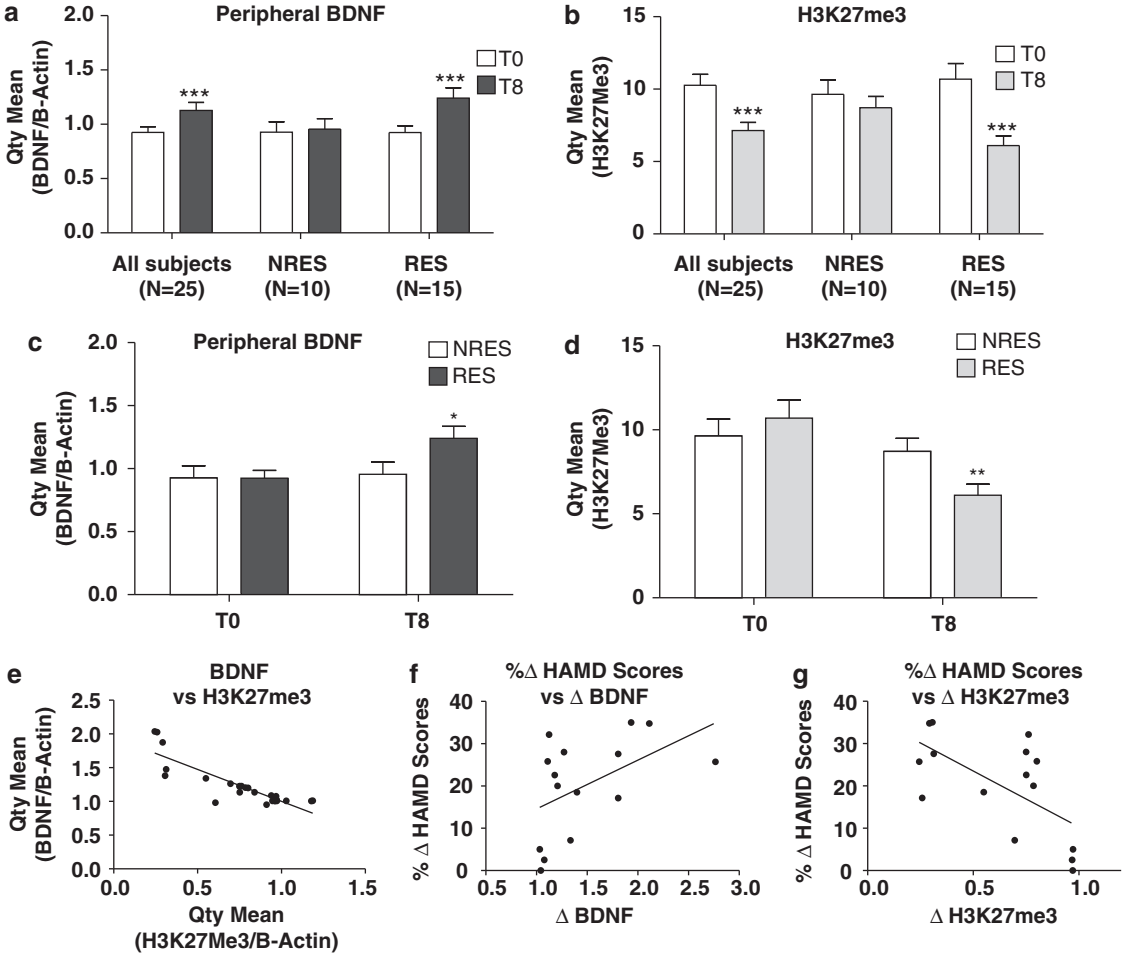

Figure 1. Epigenetic regulation of brain-derived neurotrophic factor (BDNF). (**a**, **c**) qRT-PCR AQ values of total BDNF and two endogenous controls (β-Actin and GAPDH). (**b**, **d**) Histone H3 lysine 27 trimethylation (H3K27me3) levels at BDNF IV promoter normalized to input DNA and β-Actin as controls. (**e**) Correlation between total BDNF and H3K27me3 levels. (**f**) Correlation between change in depression severity and change in BDNF expression. (**g**) Correlation between change in depression severity and change in H3K27me3 expression. Depressed patients ($N = 25$) were classified into responders (RES) and non-responders (NRES). The asterisks refer to *P*-values (*$P \leqslant 0.05$; **$P \leqslant 0.01$; ***$P \leqslant 0.001$). Variance bars represent s.e.m.

REFERENCES

1 Dwivedi Y. *Neuropsychiatr Dis Treat* 2009; **5**: 433–449.
2 Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, Prickaerts J *et al. Mol Psychiatry* 2011; **16**: 1088–1095.
3 Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. *Genomics* 2007; **90**: 397–406.
4 Boulle F, van den Hove DL, Jakob SB, Rutten BP, Hamon M, van Os J *et al. Mol Psychiatry* advance online publication, 6 September 2011; doi:10.1038/mp.2011.107.
5 Tao X, West AE, Chen WG, Corfas G, Greenberg ME. *Neuron* 2002; **33**: 383–395.
6 Martinowich K, Hattori D, Wu H, Fouse S, He F, Hu Y *et al. Science* 2003; **302**: 890–893.
7 Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. *Nat Neurosci* 2006; **9**: 519–525.
8 Chen ES, Ernst C, Turecki G. *Int J Neuropsychopharmacol* 2011; **14**: 427–429.