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Research report

BDNF Val66met polymorphism, white matter abnormalities and remission of geriatric depression

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ABSTRACT

Objective: The polymorphism BDNF val66met of the brain derived neurotrophic factor (BDNF) is common, may increase the risk for depression, and affects BDNF secretion, critical for neuronal survival, plasticity, neurogenesis, and synaptic connectivity. Our objectives were: 1) to test the hypothesis that $BDNF_{val/met}$ status influences the remission rate of geriatric depression; 2) to explore whether the relationship between BDNF allelic status to remission is influenced by the presence of microstructural white matter abnormalities.

Method: Non-demented older subjects with major depression had a 2-week placebo period, after which those with a Hamilton Depression Rating Scale (HDRS) of 18 or greater received escitalopram 10 mg daily for 12 weeks. Fractional anisotropy was determined in specific regions using the Reproducible Object Quantification Scheme (ROQS) software that operates on non-normalized data.

Results: $BDNF_{met}$ carriers were more likely to achieve remission than $BDNF_{val/val}$ homozygotes after 12 weeks of treatment with escitalopram 10 mg daily. Microstructural abnormalities in the corpus callosum, left superior corona radiata, and right inferior longitudinal fasciculum were also associated with lower remission rate. However, there were no significant interactions between $BDNF_{val66met}$ status and microstructural abnormalities in predicting remission.

Limitations: Small number of subjects, focus on a single BDNF polymorphism, fixed antidepressant dose.

Conclusions: Depressed older $BDNF_{met}$ carriers had a higher remission rate than $BDNF_{val/val}$ homozygotes. This effect was not related to microstructural white matter abnormalities, which predicted remission independently. We speculate that the relationship between $BDNF_{val66met}$ and remission is due to different effects of BDNF in brain structures related to mood regulation.

1. Introduction

Altered synaptic and structural plasticity has been proposed as one of the mechanisms of depression (Duman, 2002; Manji et al., 2001). Neurotrophins participate in the regulation of

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structural and morphological plasticity of central nervous system neurons as well as in synaptic connectivity and neurotransmission (McAllister et al., 1999; Thoenen, 2000). Among the neurotrophins, variations in the brain derived neurotrophic factor (BDNF) have been identified in several psychiatric disorders including mood disorders, schizophrenia, obsessive compulsive disorder, and Alzheimer's disease (Licinio and Wong, 2002). These observations suggest that BDNF has pleiotropic action relevant to complex behavioral disorders including depression.

BDNF has been implicated in the pathogenesis of depression and the mechanism of action of antidepressant agents (Dwivedi, 2009). Animal studies have shown that antidepressant agents increase the expression of the BDNF gene in hippocampal structures, areas related to regulation of affect and of other functions that are abnormal during depression (Nibuya et al., 1995). Further, infusion of BDNF in the dentate gyrus of the hippocampus has led to antidepressant responses in the forced swim and the learned helplessness animal models of depression (Shirayama et al., 2002). Human autopsy studies showed that antidepressants increase BDNF immunoreactivity in the dentate gyrus, hilus and supragranular regions (Chen et al., 2001). Moreover, antidepressants normalize serum BDNF levels (Aydemir et al., 2005; Gonul et al., 2005) that are reduced during depression (Karege et al., 2002). Emerging literature suggests that BDNF allelic status may influence the response of depression to antidepressants (Choi et al., 2006; Licinio et al., 2009).

BDNF is expressed by a gene on chromosome 11p13 that encodes a BDNF precursor peptide. The BDNF precursor is accumulated in the Golgi apparatus, where sortilin facilitates its correct folding into a mature domain, and after binding with carboxypeptidase E, it is sorted into a secretory pathway (Dwivedi, 2009; Lu et al., 2005). While several BDNF polymorphisms have been studied in their relationship to antidepressant response, this study focused on the single nucleotide polymorphism (rs6265) at nucleotide position 196/758 consisting of a valine (val) to methionine (met) substitution at codon 66 in the prodomain (Bath and Lee, 2006; Egan et al., 2003). There are three reasons for this choice. First, the $BDNF_{met}$ polymorphism is common (The International HapMap Project, 2003). Second, the $BDNF_{met}$ genotype has been identified as a risk factor for geriatric depression (Hwang et al., 2006; Taylor et al., 2007). Third, $BDNF_{met}$ affects activity-dependent BDNF secretion, critical for dendritic trafficking (Bath and Lee, 2006; Chen et al., 2004; Egan et al., 2003), and synaptic plasticity (Martinowich et al., 2007). Rats transfected with $BDNF_{met}$ have impaired BDNF production and distribution in several brain areas compared to rats with $BDNF_{val/val}$ genotype (Egan et al., 2003).

Late-life depression is often accompanied by white matter abnormalities (Alexopoulos, 2005). It has been proposed that white matter abnormalities compromising frontolimbic circuitry may predispose to geriatric depression and interfere with its response to pharmacotherapy (Alexopoulos, 2005). BDNF polymorphisms may influence white matter integrity in older adults since BDNF influences neuron survival, neurogenesis, and synaptic connectivity in the adult brain (Bath and Lee, 2006; Carlson et al., 2006; Egan et al., 2003). Moreover, BDNF is expressed in areas related to mood regulation, including the frontal cortex, hippocampus, striatum, and thalamus (Bath and Lee, 2006). Thus a critical question is whether promoting white matter changes is a mechanism by which BDNF allelic status influences the response of geriatric depression to antidepressants.

This analysis focused on remission rates of the subset of depressed elderly Caucasian patients participating in an escitalopram treatment trial (Alexopoulos et al., 2008) who also had genotypic characterization. Remission was selected as the outcome variable because it is viewed as the optimal target of the acute treatment of depression. Depressed patients who achieve remission are left with less disability and are three times less likely to relapse than depressed patients left with residual symptoms (Judd et al., 1998). The objectives of this analysis were: (1) to test the hypothesis that $BDNF_{val/met}$ allelic status influences the remission rate of late-life depression; and (2) to explore whether the relationship between BDNF allelic status and remission of late-life depression is influenced by the presence of microstructural white matter abnormalities.

2. Method

2.1. Subjects

The subjects were consecutively recruited individuals aged 60 years and older, who met DSM-IV criteria for unipolar major depression without psychotic features and had a score of 18 or greater on the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). After description of the study in lay terms, subjects signed written informed consent approved by the IRBs of Weill-Cornell Medical College and the Nathan Kline Institute.

Exclusion criteria were: (1) history of other axis I psychiatric disorders prior to the onset of depression; (2) presence of delirium, history of stroke, head trauma, multiple sclerosis, or brain degenerative diseases; (3) metastatic cancer, brain tumors, unstable cardiac, hepatic, or renal disease, myocardial infarction, or stroke within the 3 months preceding the study; (4) lymphoma, pancreatic cancer, or endocrinopathies other than diabetes; (5) treatment with steroids, alpha-methyl-dopa, clonidine, reserpine, tamoxifen, or cimetidine; (6) Mini Mental State Examination score <24 (Folstein et al., 1975), and (7) metal implants.

2.2. Assessment

DSM-IV diagnosis was based on the SCID-R, administered at entry to the study. Depressive symptoms were assessed using the 24-item HDRS. Cognitive impairment was rated with the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and disability with the World Health Organization Disability Assessment Scale (WHODAS-II) (Epping-Jordan and Ustun, 2000).

2.3. Treatment

The subjects had a 2-week, single-blind, placebo drug-wash-out phase at the end of which they had an MRI scan. Subjects who still met DMS-IV criteria for major depression and had HDRS ≥ 18 received controlled treatment with escitalopram 10 mg daily for 12 weeks. Subjects received their medication in 1-week supply blisters.