Accelerated age-related decrease in brain-derived neurotrophic factor levels in bipolar disorder

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Age-related conditions, such as cognitive decline, cardiovascular disease, cancer and other medical morbidities have been associated with bipolar disorder (BD) (Kapczinski et al., 2008). However the biological mechanisms underlying these associations remain unclear.

It is well established that bipolar patients show greater cognitive impairment than age-matched controls, not only during mood episodes but also during euthymia (Torres et al., 2007). Further, recent evidence suggests that growth-factor family members, particularly the brain-derived neurotrophic factor (BDNF), may play an important role in the pathophysiology of BD (Kapczinski et al., 2008; Post, 2007) and in neuroplasticity associated with ageing (Lommatzsch et al., 2005; Mora et al., 2007). Notably, BDNF is essential for long-term memory as it promotes neuronal survival and maturation. Some studies have suggested that abnormalities in the BDNF-signalling pathway might be involved in the cognitive decline observed in neuropsychiatric disorders, including Alzheimer’s (Laske and Eschweiler, 2006) and BD (Rybakowski et al., 2006). Interestingly, studies of normal ageing have shown that expression of BDNF in the hippocampus decreases with age (Hattiangady et al., 2005) and these decreases might contribute to age-related cognitive impairments (Gooney et al., 2004). To the best of our knowledge, the pattern of changes in BDNF levels in relation to age has not been examined in a clinical sample of patients with BD.

To explore this issue, we examined BDNF levels in 56 patients with bipolar I disorder and 56 healthy controls matched for age, gender and level of education. Patients were recruited from the first-episode mania programme of the University of British Columbia (UBC) Hospital, Vancouver, Canada (n=30). Patients were not in an acute mood episode according to DSM-IV criteria and the diagnosis was confirmed with structured interview. The symptomatic status was assessed within 1 wk of blood sampling with clinical rating scales such as the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale, 21-item version (HAMD-21). Subjects enrolled in both centres received open-label maintenance treatment for BD from clinicians with expertise in management of mood disorders and familiar with the most recent clinical guidelines. Patients did not have significant comorbid medical conditions and they were not on medication other than those prescribed for their psychiatric condition. Clinical variables were collected using a standardized protocol. Controls were screened to rule out any history of psychiatric disorder, neurodegenerative disorder, mental retardation, cancer or chronic/acute infection and they were not on any medication. All of the procedures described in this report have received approval from the local clinical research ethics committees. Written informed consent was obtained from all patients and healthy subjects prior to conducting any study procedures. BDNF serum levels were measured with ELISA kit (Chemicon, Temecula, CA, USA). Total protein was measured by Lowry’s method using bovine serum albumin as a standard. Results for BDNF are shown in pg/μg protein. Statistical analyses such as Pearson’s correlation followed by two-way ANOVA, were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

As expected, there was a significant negative correlation between BDNF levels and age in controls (r = −0.29, p = 0.027) as well as in patients (r = 0.70, p < 0.001) (Figure 1). Interestingly, there was a significant difference between the slopes of patients and controls (F = 14.1, d.f. = 1, 112, p < 0.001) indicating that the decrease in BDNF levels was accelerated with age in patients with BD compared with matched healthy controls. The correlation between age and BDNF levels was significant regardless of mood symptoms, in a regression model controlled for YMRS and HAMD scores (β = −0.49, p = 0.004). This suggests that BD pathophysiology may involve not only changes in
biochemistry that result in mood episodes, but also changes associated with accelerated ageing processes.

Some limitation should be considered when interpreting the results. First, BDNF levels were only assessed in the serum, however, it has been demonstrated that there is a high positive correlation \(r = 0.81\) between serum and cortical BDNF levels (Karege et al., 2002). Moreover, there is evidence that serum levels of BDNF might reflect aspects of neuronal integrity given the association with N-acetylaspartate levels (Lang et al., 2007). Second, all patients were on medication at the time of blood sampling, mostly mood stabilizers, such as lithium and divalproex. The use of these medications and improvement in symptoms has previously been reported to be associated with normalization of BDNF levels in previous studies. This would suggest that the decrease of BDNF with age would be even more marked if these patients had not been taking medication.

The finding of accelerated age-related decrease in BDNF levels in BD is in line with recent reports suggesting accelerated ageing in BD (Simon et al., 2006). Indirect evidence also comes from studies showing increased oxidative stress in BD, which is also known to increase with ageing (Andreazza et al., 2007). Notably, oxidative stress is associated with DNA damage, endothelial dysfunction and telomere shortening. These findings of accelerated age-related processes provide further support for investigating the therapeutic role of the long-term effects of agents with neurotrophic, anti-inflammatory and antioxidant properties in the treatment of BD.

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Statement of Interest

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References


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