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Elevated serum S100B protein in drug-free bipolar patients during first manic episode: a pilot study

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Abstract

S100B protein is a calcium-binding protein mostly derived from glial cells, which exerts trophic or toxic effects on neural cells depending on its concentration. Since serum S100B levels has been tested as a potential marker in neuropsychiatric disorders, and structural abnormalities on glial cells have been recently associated with bipolar disorder patients, we conducted this preliminary study to examine if S100B serum levels are altered during first manic episode. We quantitated S100B in serum of 40 subjects (20 unmedicated patients during manic episode and 20 healthy matched controls). The mean±S.D. values for S100B for bipolar subjects were 0.065±0.068 μg/l and 0.018±0.029 μg/l for healthy controls. Increased levels of S100B in bipolar mania was statistically significant (Wilcoxon signed ranks test, $Z=-2.45$, $P=0.01$). These preliminary findings suggest that mania may increase the levels of S100B in serum of bipolar disorder patients, which could be related to adaptative neural mechanisms in bipolar mania.

Keywords: Bipolar disorder; S100B protein; Mania; Serum; Mechanism of action; Glia

1. Introduction

Bipolar disorder is an heterogeneous and heritable psychiatric disorder with neurobiological findings based on psychopharmacological, brain imaging, genetic and neurochemical studies. These findings include elevated intracellular calcium concentration in lymphocytes and platelets (Hough et al., 1999; Emamghoreishi et al., 1997) induced by serotonin (Okamoto et al., 1995), cell-mediated immunity activation (Tsai et al., 1999) and abnormalities on serotonergic system genes (Vogt et al., 2000; Bellivier et al., 1998). Also, recent neuroimaging and histopathological studies in prefrontal cortex of bipolar postmortem patients have described reduced glial cells number (Drevets et al., 1998) and glial fibrillary acidic protein (GFAP) levels (Johnston-Wilson et al., 2000).

Glial cells regulate many crucial processes related to physiological neuronal activity, including regulation of neurotransmitters and extracellular ions, glucose storage, and growth factors production (Laming et al., 2000). The S100B is a gliotrophic and neurotrophic calcium-binding protein, mostly produced and released by astrocytes in the central nervous system (CNS). Extracellular S100B has been shown to exert trophic effects on neural cells

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(Schafer and Heizmann, 1996), but at higher levels may be toxic, stressing and inducing cell death by raising intracellular free calcium concentrations (Barger and Van Eldik, 1992). Regarding psychiatric disorders, elevation in serum S100B concentrations has been described both in drug-treated and drug-free schizophrenic patients (Wiesmann et al., 1999; Lara et al., 2001). Also, increased serum S100B concentration may represent a sensitive indicator of CNS damage (Persson et al., 1987) in acute ischemic stroke (Missler et al., 1997), Alzheimer disease (Griffin et al., 1989) and acute exacerbation of multiple sclerosis (Lamers et al., 1995). Moreover, transgenic mice with increased expression of S100B has been shown to be hyperactive (Gerlai and Roder, 1995), which is usually observed during manic states.

While neurotrophic factors such as brain-derived neurotrophic factor (BDNF) has received much attention in mood research, little work has addressed the role of S100B. Thus, in order to examine the possible effects of mania on S100B turnover in serum, we conducted this study. We want to examine the hypothesis that mania would increase the relative content of serum S100B concentrations in drug-free bipolar disorder patients, as observed in untreated schizophrenia subjects (Lara et al., 2001).

2. Experimental

Twenty drug-free for at least 9 months bipolar disorder patients (13 females and seven males, mean±S.D. age= 38.3±12.6 years), including 16 drug-naive patients in the first manic episode were studied. After complete description of the study to subjects, written informed consent was obtained. They did not have any current medical problems, other psychiatric disorders or history of alcohol or drug use. Major clinical (systemic diseases) and psychiatric disorders comorbidities were excluded based on detailed clinical and psychiatric history, as well as chart reviews. All patients met DSM-IV diagnostic criteria for bipolar I disorder. Also, patients' symptoms were assessed at day one (admission), using the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS). Bipolar disorder patients were in acute mania and diagnosis was confirmed independently by two psychiatrists at the time they enrolled in the study. Patients in a mixed or depressive episode were excluded.

Twenty healthy control subjects matched for age and gender (mean±S.D. age=38.3±12.2 years) were studied. They did not have any history of psychiatric disorders, substance abuse, current medical problems and did not have history of psychiatric disorders in first-degree relatives. We used the DSM-IV check-list to exclude psychiatric diagnosis in the matched controls group.

Blood samples (10 ml) were collected using vacutainer system at admission room, in the first day of hospitalization, serum was separated and kept frozen at −70 °C for no more than 6 months, until the assays were carried out. S100B protein concentrations were measured using an immunoluminometric assay (LIA-mat® Sangtec®100—Sangtec Medical, Bromma, Sweden) in a Lumat LB9507 luminometer (EG&G Berthold). All determinations were carried out within the same experiment. The S100B standard curve was linear from 0.01 to 20 ng/ml and coefficient of variation of duplicate values was within 5%.

As the data showed a skewed distribution, we took the more conservative approach and carried out a non-parametric analysis. The Wilcoxon test was used to compare nonparametrically distributed data. Correlations between YMRS and BPRS with S100B serum levels were performed using the Spearman rank order correlation test.

3. Results

Patient characteristics are described in Table 1. Bipolar patients had significantly higher S100B levels in serum samples compared to healthy control subjects (mean±S.D.=0.065±0.068 μg/l, median=0.044 and mean±S.D.=0.018±0.029 μg/l, median=0.003, respectively; $Z=-2{,}45$, $P=0.014$; see Table 1). No relationship with gender or age were found in this sample. Values lower than 0.001 were considered as 0.001 in the table. The mean length drug-free period of the non drug naïve bipolar patients was 14 months (between 9 and 24 months). There were no statistically significant differences between serum S100B levels and number of previous depressive episodes. S100B presented no correlation with BPRS ($r=0.569$, $P=0.812$) and with YMRS ($r=-0.104$, $P=0.66$) scores (see Table 1).

4. Discussion

Our preliminary findings are, to our knowledge, the first report that serum S100B levels may be increased in mania bipolar. The pathological mechanisms and correlation involved in the cross-regulation of central and peripheral levels of S100B remain unclear and should be further investigated and clarified in future studies. Nonetheless, despite minor peripheral sources cannot be ruled out as contributing sources for serum S100B, astrocytes have been proposed to represent the major source of S100B and elevations in serum levels could reflect cerebral injury or dysfunction (Missler et al., 1997). Also, studies suggest that this cytokine may induce a protective response on neural cells against an ongoing pathological process or alternatively, acting as a neurotoxic protein inducing apoptosis at higher levels (Schafer and Heizmann, 1996).

Schizophrenia and bipolar disorder have been proposed to present similar neurobiological findings related to neurochemical, pharmacological and neuroimaging studies.