S100B is increased in mood disorders and may be reduced by antidepressive treatment

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Previous studies have reported alterations of glial cells and particularly astrocytes in mood disorders. Therefore, serum concentration of the astrocytic marker S100B was ascertained with an immunoluminometric assay in 20 patients with mood disorder and 12 healthy age-matched controls. Serum S100B was elevated in major depression (median after admission 410 ng/l, at discharge $<$ 100 ng/l) and mania (130, 160 ng/l), when compared with controls ($<$ 100 ng/l; $p < 0.01$). Antidepressive treatment reduced S100B in conjunction with severity of depressive symptoms ($p < 0.01$). The severity of depression (Hamilton Depression Rating Scale) was positively correlated with S100B ($r_s = 0.51$, $p < 0.005$). Elevated serum S100B during depressive and manic episodes of mood disorders may indicate alterations of astrocytes, which are reversed by antidepressive treatment. *NeuroReport* 13:1675–1678 © 2002 Lippincott Williams & Wilkins.

Key words: Astrocytes; Bipolar disorder; Major depression; Mania; Mood disorder; S100B protein

INTRODUCTION

S100 proteins are acidic Ca^{2+}-binding proteins which may influence several cellular responses along the Ca^{2+}-signal transduction pathway [1]. The monomer S100B is found in the CNS, especially in the cytoplasm of astrocytes. S100B has a mol.wt of ~10 kDa and can form homodimers or heterodimers with S100A1. It regulates cell shape, energy metabolism, contraction, cell-to-cell communication, intracellular signal transduction and cell growth [2], and can be actively released by astrocytes [3]. Interestingly, the effects of extracellular S100B depend on its concentration [1]. Nanomolar concentrations act as growth and/or differentiation factor for neurons and astrocytes, whereas micromolar concentrations may induce apoptosis, for instance in pheochromocytoma cells. Serum S100B has been used as a marker for structural damage to the brain, particularly to astrocytes, for instance after cardiopulmonary bypass [4] and severe head injury [5]. Increased serum S100B levels may be due to leakage of the astrocytic membrane [4].

Neuroimaging studies have shown that the volume of several brain regions is decreased in mood disorders [6]. For instance, the mean gray matter volume of the subgenual prefrontal cortex is abnormally reduced in familial major depression or bipolar disorder [7], which may be due in part to reduction of glial cells [8]. Another study [9] demonstrated morphological alterations of astrocytes in the dorsolateral prefrontal cortex of patients with unipolar major depression.

In summary, serum levels of S100B may be a suitable marker for damage to the brain, and particularly for alterations of astrocytes [4]. Moreover, in mood disorders cerebral morphological abnormalities are known that include reduction of glial cells [8] and alteration of astrocytes [9], in areas of the prefrontal cortex. Therefore, we examined S100B serum levels and hypothesized that S100B is elevated in patients with major depression and mania in comparison with healthy controls, and that S100B is reduced by treatment.

MATERIALS AND METHODS

Patients consisted of nine subjects with severe major depression (age 21–69; four female) and 11 subjects with a severe manic episode of bipolar disorder (age 31–57 years; four female), who were hospitalized in the Department of Psychiatry. Depression and mania were diagnosed independently by two psychiatrists according to the criteria of the diagnostic and statistical manual of mental disorders (DSM IV) [10] and the international classification of diseases (ICD-10) [11]. The semi-structured interview according to the AMDP system (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie) and ICD-10 checklists were used for diagnosis [12]. Systemic diseases (neoplasms, autoimmune diseases, infectious diseases, cardiovascular and neurological diseases), comorbid diagnosis and drug or alcohol abuse were ruled out by taking a detailed history,

reviewing charts, physical examination and measuring body temperature, C-reactive protein, and erythrocyte sedimentation rate. Healthy controls were recruited from the medical personnel (age 34–60 years; eight female). Disorders as mentioned above and psychiatric disorders were excluded by taking a detailed history. The controls were not taking any drugs.

Patients with mood disorder were treated according to the guidelines of the American Psychiatric Association [13,14]. Treatment was not interrupted during hospitalization. There were no differences between depressive patients, manic patients and controls concerning mean ($\pm$ s.d.) age (44.4 ± 18.1, 44.2 ± 8.4, 43.8 ± 9.4 years, one-way ANOVA $df = 2$, $F = 0.01$, $p > 0.05$), total lifetime duration of illness (4.1 ± 7.1, 9.6 ± 7.3 years; 2-tailed Student's t-test $t = 1.71$, $p > 0.05$), and age at onset of first episode (40.3 ± 19.3, 34.5 ± 8.6 years; $t = -0.84$, $p > 0.05$). Only the number of episodes differed between depressive and manic patients (2.8 ± 2.2, 6.9 ± 4.1; $t = 2.89$, $p < 0.05$). The severity of depressive symptoms was assessed with the 21-item Hamilton Depression Rating Scale (HAMD) [15], and the severity of manic symptoms with the Bech-Rafaelsen Mania Scale (BRMAS) [16]. Treatment significantly reduced the severity of depression (HAMD score at admission 23.3 ± 3.1, at discharge 6.1 ± 6.6, $n = 7$; 2-tailed paired Student's t-test, $t = 5.14$, $p < 0.005$), and the severity of mania (BRMAS score at admission 19.6 ± 2.8, at discharge 3.6 ± 3.6, $n = 5$; $t = 6.64$, $p < 0.005$). The Brief Psychiatric Rating Scale (BPRS) was used additionally in patients with psychotic symptoms [17]. Clinical ratings were performed on the same or one day before/after determining S100B. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from the subjects. The research protocol was approved by the local ethics committee.

Blood samples were obtained by venipuncture from patients after admission to hospital, which was followed by approximately weekly venipuncture until discharge. Follow up was impossible in some (especially manic) patients because of lack of cooperation or discharge after < 1 week. Venipuncture was generally performed at 08.00 h. Within 2 h the serum samples were centrifuged (2°C, 3500 r.p.m., 10 min), and stored at −70°C until analysis. Serum S100B was determined with a monoclonal two-site immunoluminometric assay (LIA-mat Sangtec-100, AB Sangtec Medical, Bromma, Sweden).

Some values were below the detection limit of 100 ng/l. Therefore, we report median values and used non-parametric tests. Treatment effects were analyzed with Friedman two-way ANOVA followed by the Wilcoxon matched-pairs test. Patients and controls were compared using the Mann-Whitney test. Correlation analysis was performed according to Spearman.

RESULTS

For every patient, S100B concentration after admission to the hospital, the highest value during hospitalization and value at discharge were included in the analysis (Fig. 1). The respective highest value of S100B during hospitalization was included, because both S100B and the severity of depression increased in some patients during the initial time

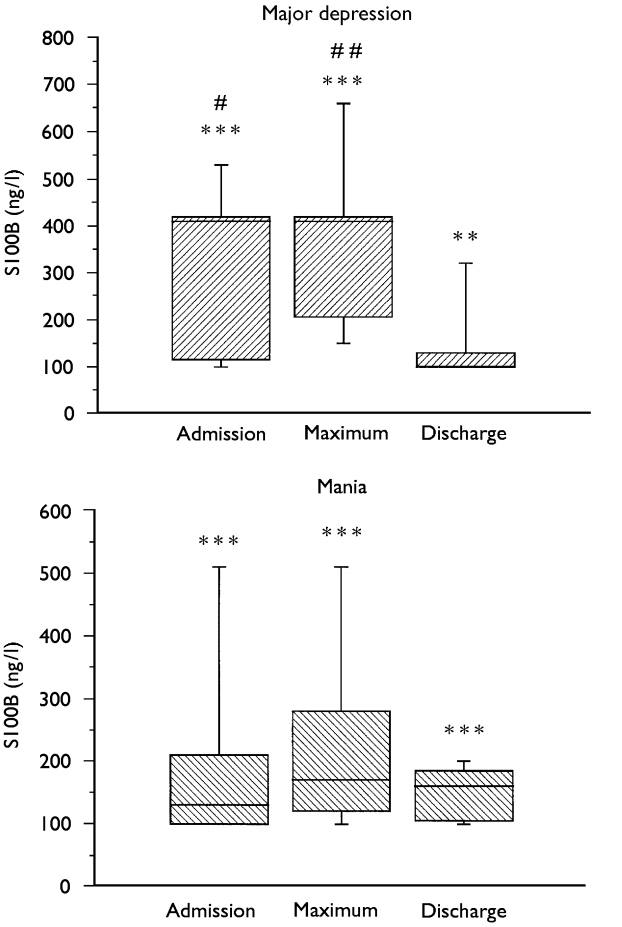

Fig. 1. S100B serum concentration in patients with major depression and mania. Box-whisker-plots for values at admission (Admission; $n = 9; 11$), highest values during hospitalization (Maximum; $n = 9; 11$), and values at discharge (Discharge; $n = 7; 5$). $\#p < 0.05$, $\#\#p < 0.01$ in comparison with values at discharge (Wilcoxon test). $**p < 0.01$, $***p < 0.001$ in comparison with healthy controls ($n = 12$; Mann-Whitney test). Values below the detection limit of 100 ng/l are reported as 99 ng/l. S100B was < 100 ng/l in all controls.

period of hospitalization. Serum S100B was below the detection limit of 100 ng/l in all 12 healthy controls. S100B values were significantly higher in depressive patients at admission (median 410 ng/l, $n = 9$, $z = -3.6$, $p < 0.001$), with respect to highest values (median 410 ng/l, $n = 9$, $z = -4.3$, $p < 0.001$), and at discharge (median < 100 ng/l, $n = 7$, $z = -2.4$, $p < 0.01$; 1-tailed Mann-Whitney test) in comparison with the controls. Serum S100B was also significantly elevated in patients with mania, when compared with S100B in the controls (median at admission 130, regarding highest values 170, at discharge 160 ng/l; $n = 11, 11, 5$; $z = -3.5, -3.8, -3.4$; $p < 0.001$, respectively).

To assess the impact of antidepressive and antimanic treatment on serum S100B, values at discharge were compared with values after admission and the respective highest values during hospitalization for both patient groups. Antidepressive treatment reduced S100B significantly in depressive patients (Friedman two-way ANOVA; $\chi^2 = 10.1$, $df = 2$, $p < 0.01$), in conjunction with decreasing

the clinical severity of depression (see above). The *post hoc* Wilcoxon matched-pairs tests revealed significantly lower serum S100B at discharge in comparison with values after admission and the respective highest values during hospitalization (1-tailed; $n=7$; $z=-1.9$, -2.4; $p=0.05$, $p<0.01$, respectively). There was no significant influence of antimanic treatment on serum S100B in patients with mania (Friedman two-way ANOVA; $\chi^2=3.9$, $df=2$, $p>0.05$). The severity of depression as rated with the HAMD correlated significantly with serum S100B in depressive patients if all measured time points were analyzed together ($r_s=0.51$, $n=31$, $p<0.005$; Spearman, 2-tailed). However, the severity of mania, as rated with the BRMAS, did not correlate with S100B ($r_s=-0.08$, $n=18$, $p>0.05$). Further, the third subscore (thought disturbance) of the BPRS was positively correlated with S100B ($r_s=0.84$, $n=6$, $p<0.05$) in depression with psychotic features.

In the following analysis, the highest S100B concentration of each case during hospitalization was related to age, number of episodes and total lifetime duration of the disorder. In mania, S100B was negatively correlated with total lifetime duration of the disorder ($r_s=-0.81$, $n=11$, $p<0.005$). If data of all patients with mood disorders were analyzed, S100B was negatively correlated with total lifetime duration of the disorder and age ($r_s=-0.45$, $r_s=-0.47$, $n=20$, $p<0.05$, respectively).

DISCUSSION

This study shows that S100B serum concentrations are increased during episodes of mood disorders when compared with healthy controls and are reduced during antidepressive treatment. Thus, our results are in accordance with literature data, which reported increased concentrations of S100B in the cerebrospinal fluid during mild or moderate depressive episodes [18], and demonstrated increased serum S100B in patients with melancholic major depression in comparison with healthy controls [19]. If one considers S100B as an astrocyte specific protein [1], data may indicate alterations of astrocytes during episodes of mood disorders which are reversed by antidepressive treatment. Interestingly, serum concentrations of neuron-specific enolase are not elevated in major depression and mania, demonstrating an intact neuronal structure ([20] and unpublished data). Results agree nicely with histopathological post mortem studies reporting alterations of glial cells [8,21,22] or astrocytes [9] in specific prefrontal brain regions of patients with mood disorders. Summarizing the studies, the assumption [21] can be supported that there is disease-specific glial pathology in mood disorders.

Two different causes may increase serum values of S100B in patients with mood disorders as found in our study. On the one hand, S100B might be increased due to injury of astrocytes and a disrupted integrity of the blood–brain barrier, as S100B, with a mol. wt of 10 kDa, may not pass through the intact blood–brain barrier [4,5]. This assumption is supported by studies showing reduced volumes [6,7], and diminished densities of glial cells [8,21,22] in several brain regions in mood disorders. Further, the blood-brain barrier is disrupted in depression as measured with the cerebrospinal fluid/serum ratio for albumin [23]. Because astrocytes induce and maintain the proper function of the blood–brain barrier [24,25], injury of astrocytes may lead to its disruption. However, increases of S100B as found in our study are relevant to astrocytes and more than just indicative of a subtle increase in permeability of the blood–brain barrier, because serum neuron-specific enolase is unchanged in major depression and mania ([20] and unpublished data).

On the other hand, serum S100B might be increased during episodes of mood disorders due to active secretion of S100B by astrocytes [1–3]. Extracellular S100B may stimulate neurite outgrowth, differentiation, or induce apoptosis, for instance in pheochromocytoma cells, depending on its concentration [1,2]. Moreover, S100B possesses autocrine functions since it stimulates astrocytic proliferation [3]. However, the action of secreted S100B is unclear as it depends on concentration [1,2]. In contrast, antidepressive drugs may reduce the release of S100B by astrocytes, since they predominantly target the adrenergic and serotonergic neurotransmitter system [9], and the serotonergic system may influence serum S100B [2].

CONCLUSION

Our results show that serum concentrations of S100B are increased during depressive and manic episodes of mood disorders. These data may suggest structural or functional alterations of astrocytes in these disorders. In contrast, antidepressive medication seems to reverse these alterations in conjunction with the reduction of clinical depression. Therefore, serum S100B can be of additional diagnostic value in mood disorders.

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