Review

S100B in schizophrenia: an update

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Abstract. Recent research has supported a potential role of immune pathology in the etiopathogenesis of schizophrenic. In the CNS various viruses were identified in the brains of schizophrenic patients. Pro-inflammatory cytokines were found to be associated with the stage of disease. Microglial cells were reported to be activated in a subgroup of schizophrenic patients in post mortem as well as imaging studies.

New research has demonstrated that astrocytes together with microglial cells are the major immunocompetent cells of the brain and play an important role in the regulation of neuronal proliferation and differentiation. S100B, a calcium binding astrocyte-specific cytokine, presents a marker of astrocytic activation.

Scientific evidence for increased S100B in acute schizophrenia is very consistent. The picture is not as clear regarding schizophrenia subtypes in acute states but patients with persistent negative symptoms or deficit syndrome show constant high S100B concentrations. There is an association between high S100B and poor therapeutic response. The increased S100B concentrations appear to be functionally relevant since they are reflected by poor cognitive performance and cross validation with other methods make it unlikely that the findings are merely an epiphenomenon. These findings suggest that the activation of astrocytes might be an important pathogenic factor for the development of schizophrenia.

Key words: S100B — Schizophrenia — Inflammation — Glia cells

Background

Recent research has supported a potential role of immune pathology in the etiopathogenesis of schizophrenia. Epidemiological studies reported an increased risk to develop schizophrenia for individuals who were in the second trimester of fetal development during an influenza epidemic (Mednick et al. 1988; Sham et al. 1992; McGrath et al. 1994). This finding is supported by a report demonstrating a 7-fold increased risk for schizophrenia in the offspring of mothers in whose blood influenza antibodies were discovered during the first trimester of pregnancy (Brown et al. 2004). It has been hypothesized that there might be a cross reaction between maternal antibodies against influenza and the fetal brain representing a pathogenic process for the development of schizophrenia later in life (Wright et al. 1993). Human endogenous retroviruses (HERVs) and Borna disease virus (BDV) are also suspected to contribute to the development of schizophrenia since higher rates of antibodies and viral sequences were discovered in patients with schizophrenic psychosis (Yolken et al. 2000; Karlsson et al. 2001; Huang et al. 2006; Bechter et al. 1997; Iwahashi et al. 1997). Elevated concentrations of proinflammatory cytokines and phagozyting macrophages in the CSF of patients point towards an inflammatory reaction in the brains of schizophrenics (Licinio et al. 1993; McAllister et al. 1995; Nikkilä et al. 1999; review: Rothermundt et al. 2001a). Also, in a subgroup of schizophrenics microglial activation has been observed with various methods (Bayer et al. 1999; Radewicz et al. 2000; Wierzba-Bobrowicz et al. 2005; van Berckel et al. 2005, 2008) although this finding is not consistent in all studies (Togo et al. 2000; Falke et al. 2000; Arnold et al. 1998; Kurumaji et al. 1997; Steiner et al. 2006b).

Considering these findings astrocytes need to be focused since apart from regulating the extracellular ionic and chemical environment they serve as immunocompetent cells within the brain. They are able to express class II major histocompatibility complex (MHC) antigens and costimula-

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tory molecules (B7 and CD40) that are critical for antigen presentation and T-cell activation. As immune effector cells they influence aspects of inflammation and immune reactivity within the brain e.g. by promoting Th2 responses. In addition, astrocytes produce a wide array of chemokines and cytokines (Dong et al. 2001).

Early studies focusing on astrocytes in schizophrenia were initiated to search for astrogliosis as a sign of neurodegeneration supporting the neurodegenerative hypothesis (Arnold et al. 1998; Arnold 1999; Falkai et al. 1999). None of these studies could demonstrate an increase of astrocyte numbers. On the contrary, Webster et al. (2001) reported a reduction of glial fibrillary acidic protein (GFAP)-immunoreactive astroglia adjacent to blood vessels of the prefrontal cortex. Rajkovska et al. (2002) also found decreased GFAP-positive astrocytes, but in layer V of the dorsolateral prefrontal cortex. In the serum of schizophrenic patients antibodies against astrocyte muscarinic cholinoceptors were reported (Borda et al. 2002).

Microarray studies revealed alterations in astrocyte- and oligodendrocyte-related genes in the brains of schizophrenic patients (Tkachev et al. 2003; Sugai et al. 2004). Matute et al. (2005) discovered a 2.5-fold increase in astrocytic glutamate transporter (GLT-1) mRNA in the prefrontal cortex of schizophrenics. Protein concentration and function of the transporter were also elevated.

The progressive brain volume reduction leading to poor clinical outcome in a subgroup of schizophrenia patients (Gur et al. 1998; DeLisi 1999; Pearlson and Marsh 1999; Lieberman et al. 2001; Shenton et al. 2001) is not caused by a loss of neurons but rather by neuronal pruning and a reduction of neuropil (Harrison 1999; Powers 1999; Selemon and Goldman-Rakic 1999; McGlashan and Hoffman 2000; Jones et al. 2002; Danos et al. 2005). Here the potential influence of glia cells has to be considered as well.

A clinical approach to assess the functionality of astrocytes in patients suffering from schizophrenia is to measure astrocytic markers that can be detected in CSF and serum. This offers the opportunity to investigate patients in various stages of disease including drug-naïve first episode patients. S100B, a protein of the EF-hand type (helix–loop–helix) with 4 Ca^{2+}-binding sites mainly produced by astrocytes, can serve as such a marker. S100B is involved in the regulation of energy metabolism in brain cells. It modulates the proliferation and differentiation of neurons and glia. Furthermore, it interacts with many immunological functions of the brain (for a review see Donato 2003; Heizmann et al. 2007; Rothermundt et al. 2004).

CSF studies

In 2004 Rothermundt et al. demonstrated increased concentrations of S100B in CSF of schizophrenia patients in an acute psychotic episode compared to matched healthy controls. Serum levels concomitantly measured were also elevated correlating closely with the CSF concentrations. Apart from the finding of increased levels in schizophrenia this study revealed that serum concentrations reliably reflect CSF concentrations not only in healthy individuals as has been shown by Nygaard et al. (1998) but also in patients suffering from schizophrenia. This finding is supported by the study of Steiner et al. (2006a) who reported elevated S100B concentrations in the CSF and serum of acute schizophrenia patients compared to healthy controls but no differences regarding GFAP, MBP or NSE. Their conclusion was that there are no hints towards a destruction of astrocytes (GFAP), oligodendrocytes (MBP) or neurons NSE) in schizophrenia. The increase in S100B therefore appears to be caused by an active secretion of S100B from astrocytes.

Serum studies

In the first published study measuring S100B in the serum of schizophrenic patients 20 patients at various stages of disease were investigated (Wiesmann et al. 1999). All patients were on neuroleptic medication. A significantly increased serum concentration of S100B was found in schizophrenic subjects compared to matched healthy controls. No correlation between S100B and age at onset or duration of illness was seen. However, S100B levels tended to be higher in patients with residual symptomatology and with long-term continuous psychotic symptoms without reaching statistical significance potentially due to a lack of statistical power.

A study on 23 schizophrenic outpatients all medicated with antipsychotic drugs (16 on clozapine) reporting significantly lower S100B concentration compared to healthy controls has to be considered with caution (Gattaz et al. 2000). Citrate plasma was used as substrate to measure S100B. However, the assay used is not designed for plasma and the S100B concentrations measured in healthy controls were almost ten times higher than the usual S100B concentrations measured in serum.

In 2001 the first data on 20 medication free schizophrenic patients were published (Lara et al. 2001). The serum of 6 outpatients and 14 patients who had just been admitted for inpatient care contained significantly higher concentrations of S100B than that of the matched healthy controls. No correlations between S100B levels and PANSS total, positive subscale or negative subscale scores could be detected. The total group showed a significant negative correlation with illness duration. However, when one outlier with an extremely high serum level (0.603 μg/l, the only drug naïve patient) was excluded from analysis the negative correlation with illness duration was not significant any more.

Rothermundt et al. (2001b) published a longitudinal study on 26 initially unmedicated or even drug naïve patients suffering from an acute episode of paranoid type schizophrenia. All patients were examined in the acute psychotic stage and after 6 weeks of neuroleptic treatment. Upon admission, the S100B serum level in schizophrenic patients was significantly higher compared to the matched healthy controls. After 6 weeks of treatment the level of significance was no longer reached. However, there was a significant positive correlation between negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking) and the S100B concentration after 6 weeks indicating that little change or even deterioration of the negative symptomatology was associated with high S100B levels. Continuously increased S100B levels were associated with the persistence of negative symptoms.

Schroeter and colleagues (2003) reported increased S100B serum concentrations in schizophrenic patients treated with antipsychotic drugs for 3 weeks while untreated patients showed normal values. Patients with deficit schizophrenia had higher S100B concentrations than non-deficit subtypes. The authors concluded that treatment with antipsychotic agents might increase S100B levels. However, since medicated and unmedicated patients belonged to different samples and were not longitudinally studied this conclusion needs to be verified.

The question whether a persistence of negative or deficit symptoms might be associated with increased S100B concentrations was focused in a study including 98 schizophrenic patients with predominant negative symptoms (Rothermundt et al. 2004). The patients were monitored for 24 weeks under standardized pharmacological treatment (risperidone or flupenthixol). S100B serum concentrations were increased throughout the whole study period in comparison to healthy controls. Those patients who showed S100B concentrations that were above the mean plus two standard deviations of the healthy controls showed decelerated therapeutic response compared to patients with lower S100B levels. It was hypothesized that an increased release of S100B might indicate an activated state of glia cells as a response to an unknown inflammatory or degenerative process.

Ryoun Kim and colleagues (2007) observed significantly higher S100B serum concentrations in long-term medicated schizophrenics compared to medication-free recent onset patients. Recent onset patients did not differ from healthy individuals with respect to S100B levels. The study by Schmitt et al. (2005) in 41 elderly chronic schizophrenic patients on stabile antipsychotic medication reproduced the increased S100B serum concentrations but saw a negative correlation with deficit symptoms.

In a very recent study Schroeter and colleagues (2009) observed increased S100B serum concentrations on admission and upon discharge in a sample of chronic schizophrenic patients containing various subtypes and medicated as well as unmedicated patients. Neuron specific enolase (NSE) was unchanged in this sample at all time points. A meta-analysis including 12 studies with n = 380 schizophrenia patients and n = 358 healthy controls revealed a high mean effect size of 2.07 ± 1.85 confirming higher S100B serum levels in schizophrenic patients (Schroeter et al. 2009).

In a treatment study administering Erythropoetin (EPO) to 39 chronic schizophrenic patients with stable disease state and medication suffering from cognitive impairment it was shown that cognitive performance significantly improved in the EPO group compared to the placebo group. Treatment with EPO and cognitive improvement were associated with a decline in S100B serum concentration.

Since negative symptoms and deficit syndrome are often accompanied by cognitive disturbance in schizophrenia a study in 75 patients was performed investigating global verbal memory (AVLT), figural memory (DCS) and abstract rule learning (LPS-3, Pedersen et al. 2008). 40 patients experienced their first episode while 35 patients suffered from chronic schizophrenia. While first episode patients and chronic schizophrenics with normal S100B serum concentration showed no cognitive deficits the chronic patients with significantly increased S100B levels were impaired in memory performance.

In a study by Rothermundt and colleagues (2007) MR-Spectroscopy was carried out in addition to S100B measurements. The rationale behind this study was to include an independent method to evaluate astrocytic activation status. Myo-Inositol is considered the glial marker in MR-Spectroscopy since it indicates energy metabolism which predominantly takes place in glia cells. In this study it could be shown that patients with increased Myo-Inositol show elevated S100B levels and vice versa. It was concluded from this study that increased S100B concentrations indeed indicate glial activation and do not have to be considered an epiphenomenon.

A new aspect regarding S100B metabolism has recently been focused by Steiner and colleagues (2008b) looking at the soluble receptor for advanced glycation products (sRAGE). RAGE, a major receptor for S100B, is located on neurons, glia and many other cell types. The actions of S100B are mainly transduced via RAGE. Soluble RAGE (sRAGE), lacking the transmembrane and signaling domains, is generated by alternative splicing (endogenous secretory RAGE/esRAGE) or by matrix-metalloproteinase induced ectodomain shedding (Geroldi et al. 2006). sRAGE is hypothesized to counteract the detrimental action of RAGE as a competitive inhibitor of the signaling pathway and as ligand scavenger, leading to renal clearance of soluble receptor-ligand complexes. In this study 26 schizophrenic patients were included. In the acute phase S100B and sRAGE were elevated in comparison

to healthy controls. After 6 weeks of treatment and psychopathological improvement S100B returned to normal while sRAGE even further increased. The authors concluded that successful treatment might lead to an increase of sRAGE to serve as a scavenger for increased S100B.

Genetic studies

In humans the gene encoding S100B is located on chromosome 21q22.3. Liu and colleagues (2005) analyzed four relevant SNPs in a sample of 384 patients with schizophrenia and 401 healthy subjects (all Han Chinese). Only rs1051169 showed a marginal association with schizophrenia. However, the haplotype V3(rs1051169)-V4(rs9722) (G-C) was significantly associated with schizophrenia in this study. Hohoff et al. (2009) investigated SNPs of the S100B gene with respect to their relevance regarding S100B mRNA and protein expression. Two SNPs (rs9722, rs11542311) of the S100B-gene were associated with S100B mRNA expression and S100B serum concentration. At least one of the SNPs included in the schizophrenia-relevant haplotype as shown by Liu et al. (rs9722) proved to be relevant regarding mRNA and protein expression in the Hohoff study.

Post mortem studies

In a post mortem study including brain tissue of 18 patients with schizophrenia Steiner and colleagues (2008a) reported more S100B-immunopositive glia in cortical brain regions of schizophrenia patients. This was the case only in the paranoid subtype while residual schizophrenics showed no significant findings. Dean et al. (2006) had reported no differences between brain homogenates (DLPF-C and OF-C) of schizophrenic and healthy subjects but did not specifically look at subtypes of schizophrenia.

Summary and conclusion

Scientific evidence for increased S100B in acute schizophrenia is very consistent. The picture is not as clear regarding schizophrenia subtypes in acute states but patients with persistent negative symptoms or deficit syndrome show constant high S100B concentrations. There is an association between high S100B and poor therapeutic response. The increased S100B concentrations appear to be functionally relevant since they are reflected by poor cognitive performance and cross validation with other methods make it unlikely that the findings are merely an epiphenomenon. Further research is needed to verify the interesting, but preliminary finding regarding sRAGE as scavenger for increased S100B.

Increased S100B concentrations in schizophrenic psychosis are currently considered to reflect glial activation. The question remains whether this activation in fact promotes pathological processes in the brain of patients with schizophrenia. It could well be possible that the activation of glia cells represents an effort of the brain to fight against an unknown pathogenic mechanism such as inflammation of unidentified origin. A persistence of astrocyte activation indicated by increased S100B concentration would then direct towards an ongoing pathogenic process not successfully limited by glial activation.

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