Potential roles of S100B in schizophrenia

Os possíveis papéis da S100B na esquizofrenia

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Abstract

Background: Scientific evidence for increased S100B concentrations in the peripheral blood of acutely ill schizophrenia patients is consistent. In the past, this finding was mainly considered to reflect astroglial or blood-brain barrier dysfunction. **Methods:** Using Entrez, PubMed was searched for articles published on or before June 15, 2011, including electronic early release publications, in order to determine other potential links between S100B and current hypotheses for schizophrenia. **Results:** S100B is potentially associated with the dopamine and glutamate hypotheses. Supporting the glial hypothesis, an increased expression of S100B has been detected in cortical astrocytes of paranoid schizophrenia cases, while decreased oligodendrocytic expression has been observed in residual schizophrenia. Recently, the neuroinflammation hypothesis of schizophrenia has gained attention. S100B may act as a cytokine after secretion from glial cells, CD8+ lymphocytes and NK cells, activating monocytes and microglial cells. Moreover, S100B exhibits adipokine-like properties and may be dysregulated in schizophrenia due to disturbances in insulin signaling, leading to the increased release of S100B and free fatty acids from adipose tissue. **Discussion:** Dysregulation of pathways related to S100B appears to play a role in schizophrenia. However, S100B is expressed in different cell types and is involved in many regulatory processes. Currently, "the most important" mechanism related to schizophrenia cannot be determined.

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Keywords: Schizophrenia, astrocyte, oligodendrocyte, glia, neuropil, neurodegeneration, dopamine, glutamate, blood-brain barrier, lymphocyte, NK-cell, adipocyte, glucose, insulin.

Resumo

Contexto: Evidências científicas do aumento da concentração da proteína S100B no sangue de pacientes esquizofrênicos são muito consistentes. No passado essa informação era principalmente considerada como reflexo da disfunção astroglial ou da barreira hematoencefálica. **Métodos:** Pesquisa de publicações no PubMed até o dia 15 de junho de 2011 visando estabelecer potenciais ligações entre a proteína S100B e as hipóteses correntes da esquizofrenia. **Resultados:** A S100B está potencialmente associada com as hipóteses dopaminérgica e glutamatérgica. O aumento da expressão de S100B tem sido detectado em astrócitos corticais em casos de esquizofrenia paranoide, enquanto se observa uma redução da expressão em oligodendrócitos na esquizofrenia residual, dando suporte à hipótese glial. Recentemente, a hipótese da neuroinflamação da esquizofrenia tem recebido atenção crescente. Nesse sentido, a S100B pode funcionar como uma citocina secretada por células gliais, linfócitos CD8+ e células NK, levando à ativação de monócitos e microglia. Além disso, a S100B apresenta propriedades do tipo adipocina e pode estar desregulada na esquizofrenia, devido a distúrbios da sinalização de insulina, levando ao aumento da liberação de S100B e ácidos graxos do tecido adiposo. **Conclusão:** A expressão de S100B em diferentes tipos celulares está envolvida em muitos processos regulatórios. Atualmente, não pode ser respondido qual mecanismo relacionado à esquizofrenia é o mais importante.

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Palavras-chave: Esquizofrenia, astrócito, oligodendrócito, glia, neurópilo, neurodegeneração, dopamina, glutamato, barreira hematoencefálica, linfócito, célula NK, adipócito, glicose, insulina.

S100B, a member of the S100/calmodulin/troponin protein family

S100 proteins belong to a multigenic family of small (~10-kDa) proteins, including calmodulin and troponin, which are characterized by two calcium-binding sites with helix-loop-helix ("EF-hand type") conformations. The name is derived from the fact that these proteins are soluble in 100% ammonium sulphate at neutral pH[1]. At present, at least 25 members of this family, which are exclusively expressed in vertebrates, have been identified. Of these, 21 family members (S100A1–S100A18, trichohyalin, filaggrin and repetin) have genes clustered on chromosome locus 1q21, while other S100 proteins are found on chromosome loci 4p16 (S100P), 5q14 (S100Z), 21q22 (S100B) and Xp22 (S100G) in humans[2,3]. These proteins are calcium (Ca^{2+}) sensor proteins, which interact with intracellular target proteins, thereby regulating their activities. It should be noted that the Ca^{2+}-binding affinity of S100 proteins is lower than that of the universal intracellular Ca^{2+} sensor protein calmodulin[4].

S100B was the first member of the S100 protein family to be identified (former synonyms are S100 and S-100). It consists mostly of S100 ββ homodimers, but the heterodimer formation of β subunits with S100 α1 has also been observed *in vitro*[5]. The protein is abundant in astroglial and oligodendroglial cells and has therefore been considered a glial marker protein[6-8]. The ependyma, choroid plexus, and certain neuronal populations also appear to express S100B[6]. Due to its high expression in brain tissue, most neurodegeneration-related S100 studies have focused on S100B in particular. S100B interacts with a number of intracellular growth-associated target proteins, such as growth-associated protein 43 (GAP-43), the regulatory domain of protein kinase C (PKC), the anti-apoptotic factor Bcl-2 and the tumor suppressor protein p53[9]. In addition, S100B has been implicated in the regulation of intracellular processes and is also a secreted protein

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that exhibits cytokine-like activities, which mediate interactions among glial cells and between glial cells and neurons. These effects are induced, in part, by the interaction of S100B with the receptor for advanced glycation end products (RAGE), a multiligand receptor that has been shown to transduce inflammatory stimuli and the effects of several neurotrophic and neurotoxic factors[10].

S100B-related findings in schizophrenia patients

Recently, it has been suggested that S100B plays a role in the pathogenesis of schizophrenia. This is exemplified by the following studies[11-13]:

Genetics and serum studies

S100B is a susceptibility gene for bipolar disorder with psychosis, schizophrenia and cognitive dysfunction[14-16]. Various studies have shown that blood levels of S100B are increased in schizophrenia[11,17-19], as summarized in a recent meta-analysis of 13 studies involving 420 patients with schizophrenia and 393 control subjects[7]. Serum S100B reaches high effect sizes in schizophrenia patients compared to controls (mean ± SD: 2.02 ± 1.78), as confirmed by including only studies investigating drug-free patients (mean ± SD: 1.94 ± 1.33; n = 7). Moreover, elevated S100B levels were partly correlated with acute exacerbations and the severity of negative symptoms[11,18,20-22].

CSF studies

In 2004, Rothermundt *et al.* demonstrated increased concentrations of S100B in the cerebrospinal fluid (CSF) of patients with schizophrenia during an acute psychotic episode, as compared to matched healthy controls[17]. Serum concentrations, measured concomitantly, were also increased and correlated closely with CSF concentrations. This finding is supported by a study from Steiner *et al.* that reported increased S100B concentrations in the CSF and serum of acute first onset schizophrenia patients compared to healthy controls, but showed no differences in the concentrations of glial fibrillary acidic protein (GFAP), myelin basic protein (MBP) or neuron specific enolase (NSE). These findings were interpreted as an indirect indicator of increased active secretion of S100B from glial cells[23].

Post-mortem and magnetic resonance spectroscopy studies

It has been suggested that elevated S100B concentrations in the serum and CSF of patients with schizophrenia indicate astrocyte activation or oligodendroglial loss[11,17,18,24]. Accordingly, a recent stereologic postmortem study reported higher densities of S100B-positive cells, which were mainly astrocytic, in the cortical brain regions of patients with paranoid schizophrenia. In addition, there was a loss of S100B-positive glial cells, which were primarily oligodendrocytic, in the adjacent white matter regions of patients with residual schizophrenia[25]. These findings were particularly pronounced in the dorsolateral prefrontal cortex and the adjacent white matter. Moreover, patients with increased S100B concentrations showed increased concentrations of the putative gliosis marker myo-inositol, using *in vivo* magnetic resonance spectroscopy[26].

Potential links between S100B and the pathogenesis of schizophrenia

Previous studies suggest several theories as to how S100B could be involved in the pathophysiology of schizophrenia (see Table 1).

The dopamine hypothesis was established first. It proposed that hyperactivity of dopaminergic transmission was responsible for the disorder[27]. This was based on the observation of the psychotogenic effects of dopamine-enhancing drugs, such as amphetamines and cocaine, while dopamine D2 receptor blockers showed therapeutic efficacy on psychotic symptoms of acutely ill schizophrenia patients. Subsequently, the hypothesis was modified to better explain the negative symptoms. As a result, an imbalance in dopaminergic neurotransmission with hyperactive subcortical mesolimbic projections (resulting in the hyperstimulation of limbic D2 receptors and positive symptoms) and hypoactive mesocortical DA projections to the PFC (resulting in the hypostimulation of cortical D1 receptors, negative symptoms, and cognitive impairment) has become the predominant hypothesis[28]. Interestingly, recent cell culture experiments and binding assays by Liu *et al.*[29] have shown that S100B may enhance dopaminergic neurotransmission by binding to the third cytoplasmic loop of the D2 receptor. Therefore, increased expression of S100B may be directly linked to the dopamine hypothesis of schizophrenia. However, future studies of psychoses in animal models are necessary in order to clarify whether this mechanism is contributing to a hyperactive dopaminergic system in limbic brain regions, which has been observed in schizophrenia.

Table 1. Potential links between alterations in S100B and hypotheses of schizophrenia pathogenesis

Dopamine hypothesis	Binding of S100B to the 3rd cytoplasmic loop of the D2-receptor → increased dopamine signal transduction [cell culture experiments and binding assays[29]]
Glutamate hypothesis	S100B enhances glutamate uptake into astrocytes → reduced synaptic concentration of glutamate; glutamate inhibits the release of S100B from astrocytes [cell culture experiments[33,34]]
Neurodegeneration hypothesis	Elevated concentrations of S100B → neuronal apoptosis [cell culture experiments[38]]
Glial hypothesis	Increased astroglial S100B expression and release in paranoid schizophrenia → astroglial activation [human postmortem brain tissue[25]; cerebrospinal fluid from early onset paranoid schizophrenia cases[23]], Loss of S100B expressing oligodendrocytes in residual schizophrenia → impaired myelin integrity and oligodendrocyte degeneration [human postmortem brain tissue[25]]
Reduced neuropil hypothesis	Elevated concentrations of S100B → rarefication of dendrites and synapses [transgenic mice overexpressing S100B[40]; cell culture experiments[38]]
Neuroinflammation hypothesis	S100B activates cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression in microglial cells [cell culture experiments[51,52]], Human CD8+ T cells and NK cells express and secrete S100B upon stimulation [flow cytometry and cell culture experiments[53]] S100B is a potential marker of blood-brain barrier dysfunction [animal experiments and magnetic resonance imaging after osmotic blood-brain barrier disruption[50]]
Impaired glucose utilization hypothesis	S100B may increase intracellular energy supply by activating glycolysis (fructose-1,6-bisphosphate aldolase) and glycogenolysis (phosphoglucomutase) [binding assays[71,72]] Association of increased blood levels of S100B with insulin resistance [serum analyses in schizophrenia patients[64]], release of S100B from adipose tissue is regulated by fasting, insulin and adrenalin [animal and cell culture experiments [60,62,80,81]] Cerebral deficiency in glucose supply → increased S100B release from astro- and oligodendroglial cells/glucose oversupply → reduced S100B production and secretion in astrocytes [cell culture experiments[8,67,68]]

The glutamate hypothesis is the second most frequent neurotransmitter hypothesis of schizophrenia. It postulates that the N-methyl-D-aspartate (NMDA) glutamate receptor function is compromised. Glutamate is the major excitatory neurotransmitter in the central nervous system. Nearly half of the neurons in the brain, including all neurons that project from the cerebral cortex, are believed to use glutamate as their neurotransmitter. Glutamate receptors are classified into two broad categories: ionotropic and metabotropic receptors. Ionotropic glutamate receptors, which include NMDA, kainate, and AMPA subtypes, initiate rapid depolarization by facilitating sodium or calcium entry into neurons through channels formed by the receptor itself. Metabotropic glutamate receptors modulate neurotransmission by activating G-protein coupled synaptic transduction mechanisms. The idea of a glutamatergic abnormality in schizophrenia was first proposed by Kim *et al.* in 1980[30], based on their findings of low cerebrospinal fluid (CSF) glutamate levels in patients with schizophrenia. Model psychosis research has shown that administration of NMDA receptor antagonists, such as phencyclidine (PCP) or ketamine, produces schizophrenia-like positive, negative and cognitive symptoms in healthy individuals and exacerbates preexisting symptoms in patients with schizophrenia[31]. Interestingly, the glutamate and dopamine systems are linked through neuroanatomic pathways. For example, bursting of dopamine neurons is dependent on the activation of NMDA receptors on these neurons[32]. Astrocytes may interfere with glutamatergic neurotransmission in cortical brain areas because they are an integral part of the so-called tripartite synapse. The tripartite synapse involves the pre- and postsynaptic terminals of two neurons and a neighboring astrocyte that is involved in both the uptake of glutamate from the synaptic cleft and its recycling to glutamine, which is then shuttled back to the presynaptic neuron. Interestingly, recent cell culture experiments have shown that S100B enhances the uptake of glutamate into astrocytes[33]. Therefore, S100B could improve the recycling of glutamate in schizophrenia. Contrarily, another study has demonstrated that glutamate inhibits the release of S100B from astrocytes[34]. In conclusion, an increased S100B release from astrocytes may arise in schizophrenia patients due to reduced availability of glutamate, as a counterregulatory mechanism.

In agreement with Emil Kraepelin's historical concept of dementia praecox[35], about 60% of all schizophrenia patients suffer from a cognitive decline and residual symptoms during the long-term disease course. Therefore, the neurodegeneration hypothesis has been proposed and is supported by magnetic resonance imaging studies, indicating that characteristic findings, like ventricular enlargement and total gray matter loss, have a progressive component[36,37]. Interestingly, it has been shown that micromolar concentrations of S100B may induce neuronal apoptosis in cell culture, suggesting that S100B could be involved in such neurodegenerative processes[38]. However, this idea is questionable, since the S100B concentrations tested in cell culture were unphysiologically high. The subtle, yet well-documented, volume reductions seen, especially in association cortex (prefrontal, temporal, parietal) and limbic structures (hippocampus, parahippocampal gyrus) of schizophrenia patients, are not associated with a loss of neurons[39]. This raises the question as to whether connecting elements between the neurons (i.e., axons, dendrites, synapses) and glial cells are the main focus of histopathology. In line with the reduced neuropil hypothesis of schizophrenia, Whitaker-Azmitia *et al.*[40] observed a significant loss of dendrites and synapses in transgenic mice overexpressing S100B. The glial hypothesis of schizophrenia is based on findings of abnormal expression of several astrocyte- and myelin/oligodendrocyte-related genes, as well as on reports of a reduced number of oligodendrocytes, which might explain the white matter abnormalities and disturbed inter- and intrahemispheric connectivities that are frequently described in schizophrenia[39,41-43]. S100B is probably connected to the glial hypothesis, since there is histological evidence for an activated expression of this protein in cortical astrocytes of patients with paranoid schizophrenia[23,25]. Notably, S100B has also been found in immature oligodendrocytes and is partly colocalized with myelin sheaths[6]. Residual schizophrenia cases showed a loss of S100B immunopositive oligodendrocytes in white matter regions adjacent to the anterior cingulate, dorsolateral prefrontal, orbitofrontal, and superior temporal cortices[25]. This finding may be interpreted as another indication of oligodendrocyte dysfunction in schizophrenia cases with prominent deficit symptoms.

There is growing evidence for an immune component in a subgroup of schizophrenia patients. Alterations in cytokine expression patterns[44], such as increased levels of peripheral blood interleukin-1 receptor antagonist (IL-1RA), soluble interleukin-2 receptor (sIL-2R), and interleukin-6 (IL-6), as well as a shift from T- to B-cell-mediated immunity[45] have been observed. Moreover, several immune-related susceptibility genes for schizophrenia have been identified in the major histocompatibility complex (MHC) region of chromosome 6p21.3-22.1[46]. The neuroinflammation hypothesis of schizophrenia is further supported by previous postmortem and positron emission tomography studies which have suggested microglial activation during acute disease phases[47-49]. It remains unclear whether the recruitment of peripheral blood monocytes contributes to such increases in microglial density. Therefore, it would be of interest to learn more about the function of the blood-brain barrier. Animal experiments and human studies have shown that blood levels of S100B increase after osmotic blood-brain barrier disruption[50]. However, serum S100B is probably not specific enough for blood-brain barrier integrity, since S100B expression has been described in many extracranial tissues, including adipocytes, chondrocytes, dendritic cells, Langerhans cells, injured myocardium, satellite cells of dorsal root ganglia, and Schwann cells of the peripheral nervous system[6]. Interestingly, cell culture experiments indicate that S100B might function as an interface with immunological processes, distinct from known cytokine- and chemokine-mediated pathways. The increased release of S100B from astro- or oligodendroglia may contribute to neuroinflammatory processes by activating microglial cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression[51,52]. Apart from glial cells, CD8+ lymphocytes and NK cells may also release S100B, which is then capable of activating monocytes by upregulating CD11b and membrane shedding of CD62L[53]. Further studies are needed in order to clarify the significance of these aforementioned potential links between S100B and the immune system in schizophrenia.

Recent studies have led to novel interpretations of previous S100B findings, in the context of disturbances in glucose metabolism in schizophrenia[54]. Schizophrenia is characterized by a 20% higher mortality rate than in the general population. Important contributing factors are an increased risk for type 2 diabetes and metabolic syndrome (defined by the American Heart Association as the presence of three or more of the following components: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, prothrombotic state, or proinflammatory state). Weight gain and impaired glucose tolerance have been mainly attributed to side effects of atypical antipsychotic medication, such as clozapine and olanzapine. However, impaired fasting glucose tolerance has also been reported in drug-naïve schizophrenia cases and unaffected siblings, suggesting disease-inherent abnormalities in peripheral glucose metabolism[4]. Adipocytes are an important source of serum S100B since the concentrations of adipose S100B are similar to those found in the nervous system tissue[55-58]. S100B is closely linked to the regulation of cellular energy metabolism. An immunoelectron microscopic study suggested that S100B may be involved in the regulation of lipolysis[59]. The release of S100B from adipocytes is reduced by insulin, and activated by physiological factors such as stress (catecholamines and adrenocorticotropic hormone (ACTH)) or fasting[60-62]. Given the increased prevalence of obesity and metabolic syndrome in patients and their first degree relatives, an increase in adipose tissue mass or changes in insulin metabolism, such as insulin resistance are likely to play a major role in increased S100B levels in schizophrenia. Indeed, a recent study showed a close correlation between body mass index (BMI) and adipocyte-type fatty acid-binding protein with serum S100B levels in healthy human subjects[63]. A second serum study in acutely ill schizophrenia patients showed that elevated S100B levels were associated with visceral obesity and insulin resistance[64]. Cerebral insulin signaling also seems to be affected in schizophrenia[65,66], probably causing disturbances in neural glucose uptake and utilization, as revealed by measurements of elevated CSF glucose levels, *in vivo* fluorodeoxyglucose positron emission tomography (FDG-PET) and functional magnetic resonance imaging (fMRI) studies[54]. Interestingly, the expression of S100B in astro- and oligodendroglia, and its release from these cells, are activated by glucose deprivation and inhibited by glucose oversupply[8,67,68]. Moreover, like in adipocytes (see above), insulin has been shown to downregulate S100B expression in astrocyte cultures and rat brain[69,70]. Since S100B binds to fructose-1,6-bisphosphate aldolase and phosphoglucomutase, it may improve intracellular energy balance by modulating glycolysis and glycogenolysis[71,72].

Influence of antipsychotic drugs on S100B levels

Antipsychotic drugs and nonglial cellular sources of S100B may also influence concentrations of S100B in bodily fluids. Cross-sectional clinical studies have shown both increased and decreased levels of S100B in the blood of patients taking antipsychotic medication[73]. Rothermundt *et al.*[17] reported that compared to age- and sex-matched healthy controls, schizophrenic patients had significantly increased levels of S100B in their serum, both upon admission and after 12 or 24 weeks of treatment with risperidone or flupenthixol. The level of S100B in serum from these patients did not change between these time points. Steiner *et al.*[22] and Ling *et al.*[74] observed higher baseline levels of S100B in schizophrenic patients compared to levels after 6 or 12 weeks of treatment, suggesting that antipsychotic medication could decrease S100B levels in schizophrenic patients.

As recently summarized[54], glial cell culture experiments have shown that antipsychotic drugs can directly affect glial S100B release. Increased amounts of S100B were found in the extracellular medium of astroglial C6 cells treated with high doses of risperidone[75]. In contrast, treatment of astroglial C6 and oligodendroglial OLN-93 cells with haloperidol and clozapine, at concentrations corresponding to the assumed therapeutic dose range of these drugs, reduced the release of S100B *in vitro*[73]. Other S100B-expressing cell types, like adipocytes, have not yet been tested in this context.

Alternatively, the potential influence of atypical antipsychotics on S100B levels, via changing metabolic factors, should be considered a more indirect mechanism[54]. Among the second generation antipsychotics, clozapine and olanzapine are associated with the highest risk of weight gain, as well as changes in insulin sensitivity and lipid metabolism, which, in turn, increase the risk of diabetes and cardiovascular disease[76-78]. In the future, well-controlled clinical studies will be necessary in order to test a possible interference of these metabolic side effects on S100B levels.

Summary and conclusion

Scientific evidence for increased S100B in acutely ill schizophrenia patients is very consistent. The picture is not as clear regarding schizophrenia subtypes in acute states or for the effects of antipsychotic medication, but patients with persistent negative symptoms or deficit syndrome show high S100B concentrations. In the past, increased S100B concentrations in schizophrenic psychosis were mainly considered to reflect astroglial or blood-brain barrier dysfunction.

This review confirms that increased S100B production and release from activated or dysfunctional glial cells may interfere with the neurodegeneration, glial and reduced neuropil hypotheses. Moreover, this review attempts to broaden the perspective with regard to how S100B is potentially linked with other concepts, *e.g.*, current neurotransmitter theories, such as the dopamine and glutamate hypotheses. Supporting the glial hypothesis, an increased expression of S100B has been detected in cortical astrocytes of paranoid schizophrenia cases, while decreased oligodendrocytic expression has been observed in residual schizophrenia. Recently, the neuroinflammation hypothesis of schizophrenia has gained growing attention. S100B may act as a cytokine after secretion from glial cells, CD8+ lymphocytes and NK cells, activating monocytes and microglial cells. Moreover, S100B exhibits adipokine-like properties and may be dysregulated in schizophrenia due to disturbances in insulin signaling, leading to the increased release of S100B and free fatty acids from adipose tissue. In summary, S100B is expressed in different cell types and is involved in many regulatory processes. Currently, "the most important" mechanism related to schizophrenia cannot be determined.

S100B is not suitable as a differential diagnostic biomarker, since elevated serum levels have been observed in many neuropsychiatric disorders[13]. Increased serum S100B concentrations have also been observed in major depression and bipolar disorder[7]. Therefore, S100B may only be useful in combination with other proteins and metabolites in order to create a diagnostic biomarker signature of schizophrenia[79].

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Conflict of interest

None declared.

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