Archives of Epilepsy

Review

# The S100B Protein in Epilepsy

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**Cite this article as:** Seçen AE, Akçalı DT, Kurt G. The S100B Protein in Epilepsy. *Arch Epilepsy.* 2023;29(2):37-40.

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**Received:** 26.05.2023 **Accepted:** 02.06.2023 **Publication Date:** 09.06.2023
DOI: 10.4274/ArchEpilepsy.2023.231289



**Abstract**

Epilepsy is a chronic disease caused by an increased excitability of nerve cells in the brain, characterized by two or more unprovoked seizures, which can be attributed to genetic or acquired causes. There are currently more than 50 million people worldwide who have epilepsy, and this number is continuously increasing. Although significant advancements have been made regarding the diagnosis and treatment of epilepsy in recent years, our knowledge about the cellular and molecular mechanisms underlying the development of epilepsy or epileptogenesis is still insufficient. The absence of a specific biomarker for diagnosis makes epilepsy relatively challenging to diagnose. Therefore, the discovery and implementation of specific markers are important for the diagnosis and early treatment of epilepsy. The S100 protein family is a group of low molecularweight proteins that are localized in the cytoplasm and/or nucleus of various cells. These proteins play a regulatory role in various intracellular processes, including the cell cycle, by localizing within the cytoplasm and nucleus of the cell. S100B is a member of the S100 family. Its functions are highly concentration-dependent, at physiological concentrations, it exhibits a neuroprotective function, supporting neural survival and stimulating dendrites and axons. However, at high concentrations, it induces neuronal apoptosis, activates pro-inflammatory cytokines, and stress-induced inflammatory enzymes. When brain cells are damaged or destroyed, S100B proteins are released from the cells and can be detected in the blood. S100B can be considered as a prognostic biomarker that can be used for diagnosing epilepsy in clinical practice. This review summarizes the role of the S100B protein in epilepsy.

**Keywords:** Biomarker, epilepsy, S100B

## INTRODUCTION

Since antiquity, epilepsy has been a known and researched disease. Even though Hippocrates and Galen maintained that epileptic seizures developed because of various etiologies in the brain, epilepsy had always been attributed to supernatural causes until philosophers and physicians in the 19th century began conducting research on brain function.[1] Because of all these studies, epilepsy is now defined as a chronic disease caused by an increased excitability of nerve cells in the brain (neuronal hyperexcitability), characterized by two or more unprovoked seizures, which can be attributed to genetic or acquired causes.

Epilepsy is a common neurological disorder that can affect individuals of all age groups. There are currently more than 50 million people worldwide who have epilepsy; nearly 80% of them live in low- and middle-income countries. This number is continuously increasing, with approximately 2.4 million people being newly diagnosed each year.[2] Although significant advancements have been made regarding the diagnosis and treatment of epilepsy in recent years, our knowledge about the cellular and molecular mechanisms underlying the development of epilepsy or epileptogenesis is still insufficient.[3]

Although monotherapy is sufficient for seizure control in most epilepsy patients, seizures cannon be effectively controlled in 30% of patients despite the availability of over 20 types of antiepileptic drugs.[4] Some patients may require combination therapy, resective surgery, or neurostimulation device application. Due to comorbid mood and psychiatric disorders, cognitive deficits, and the side effects of drugs used during treatment, epilepsy can significantly impair the quality of life. In addition, seizures can be fatal due to their direct effects on autonomic and arousal functions and the indirect effects caused by suffocation or other accidents that may occur during seizures.

One of the biggest obstacles hindering the development of treatment options in epilepsy is the heterogeneity of epilepsy. Different genetic and pathophysiological factors [such as stroke, traumatic brain injury (TBI), perinatal and prenatal injuries, central nervous system (CNS) malformations or tumors] may be underlying causes of epilepsy seizures.[1] The presence of so many different factors indicates that different

mechanisms can cause epileptogenic focus and that there are potentially different mechanisms of functional impairment and seizure formation.

The absence of a specific biomarker for diagnosis makes epilepsy relatively challenging to diagnose. No biomarker has yet been found that can be used to reliably assess epileptogenesis. Pitkänen and Engel[1] have defined a biomarker that can be used for epileptogenesis as "an objectively measurable characteristic of a biological process that reliably identifies the development, presence, severity, progression or localization of an epileptogenic abnormality". Therefore, the discovery and implementation of specific markers are important for the diagnosis and early treatment of epilepsy.[4,5]

**S100 Proteins**

The S100 protein family is a group of low-molecular-weight proteins that is localized in the cytoplasm and/or nucleus of various cells in vertebrates and contains two calcium-binding regions in a helix-loop-helix structure. They are involved in the regulation of various cellular processes, including cell cycle progression and differentiation. The S100 family proteins consist of two subunits, alpha and beta, and exist as homo or heterodimers depending on the subunit status. However, they typically exhibit homodimeric structure. Dimerization of S100 proteins is significant in terms of displaying their biological activities. When $Ca^{2+}$ binds, the helix structure changes.[6,7] The $Ca^{2+}$ binding region of each S100 monomer contains a separate binding region for the target protein. Binding of these target proteins to the S100 proteins produces a strong reduction of the S100 protein. This is due to the structural changes of the helices.[8,9]

S-100 proteins are found in cells originating from the neural crest (Schwann cells, melanocytes, and glial cells), chondrocytes, adipocytes, myoepithelial cells, macrophages, Langerhans cells, dendritic cells, and keratinocytes.[10] They have many intracellular and extracellular regulatory activities. These proteins play a regulatory role in various intracellular processes including the cell cycle by localizing within the cytoplasm and nucleus of the cell. Proteins in the S100 family regulate the enzymatic activities by interacting with numerous effector proteins, influence the structural dynamics of the cytoskeleton, regulate cell growth-differentiation, motility and cell cycle, as well as maintain $Ca^{2+}$ homeostasis.[11] Extracellular S100 proteins act as regulators in inflammatory cells, neurons, astrocytes, microglial, endothelial, and epithelial cells. Ultimately, S100 proteins are multifunctional proteins involved in the regulation of various cellular activities.[12,13]

The S100 protein genes consist of at least 13 members located as a cluster on chromosome 1q21. However, the S100B gene is located on 21q22.3.

**MAIN POINTS**

- When brain cells are damaged or destroyed, S100B proteins are released from the cells and can be detected in the blood. This protein has also been shown to increase in blood and cerebrospinal fluid especially after seizures.
- It is believed that S100B can be considered as a biomarker that can be used for epilepsy in clinical practice.

**S100B**

S100B, a 21 kDa protein, is a member of the S100 family. The alpha- and beta-beta heterodimers are defined as S100B proteins. It functions as a $Ca^{2+}$ receptor inside the cell and as a neuropeptide outside the cell. The alpha-beta isoform is in glial cells, whereas the beta-beta isoform is found in brain astrocytes and Schwann cells. The S100B protein is the most abundant member of the S100 protein family in the CNS, accounting for 96% of total S100 proteins in human brain.[14-16]

It is considered to be specific to glial cells and is thought to be primarily expressed in astrocytes. When produced and released by astrocytes at physiological concentrations, it has a neurotropic effect on nerve regeneration and development. In addition to regulating intracellular signal transmission, intercellular communication, energy metabolism, and cell growth, it exerts autocrine and paracrine effects on neurons and glial cells. This protein is believed to play a regulatory role in axon elongation, stimulation of calcium influx, inhibition of protein kinase C-mediated phosphorylation, astrocytosis, and inhibition of axonal proliferation and intracellular microtubule formation. It exhibits neurotropic behavior in the developing central nervous system, stimulating cell proliferation and migration within the cell, while inhibiting apoptosis and differentiation. This is important for brain development and repair. It also functions in the regulation of certain enzymes. The extracellular activities of S100B are effective on neurons, astrocytes, microglia, macrophages and other cells.[14,16,17]

The increase in intracellular $Ca^{2+}$ and $Zn^{2+}$ concentrations causes the release of S100B from glial cells into the extracellular environment via vesicular transport. S100B displays cytokine-like functions in the extracellular environment.[18] These functions are highly concentration dependent; at nanomolar (nM) levels, it exhibits a neuroprotective function supporting neural survival and stimulating dendrites and axons. However, at micromolar (μM) concentrations, it induces neuronal apoptosis, activates pro-inflammatory cytokines, and stress-induced inflammatory enzymes.[19-21] In other words, it has dose-dependent neurotropic or neurotoxic effect. These effects occur via receptor for advanced glycation end products (RAGE) in the brain. S100B produces its neurotoxic effect by inducing apoptosis. μM concentrations of S100B interact with RAGE leading to an increase in ROS. As a result, cytochrome-C is released, inducing the caspase cascade and resulting in apoptotic neuronal cell death. It also induces apoptosis by increasing the permeability of L-type $Ca^{2+}$ channels and 'up-regulating' a series of apoptosis genes (c-fos, c-jun, bax, bcl-x).[22-26]

When brain cells are damaged or destroyed, S100B proteins are released from the cells and can be detected in blood.[27] In cases of brain injury and neurodegenerative diseases, they activate astrocytes.[17]

When the cytosol of the glial and Schwann cells is structurally damaged, the S100B protein is released into the cerebrospinal fluid (CSF) and bloodstream. In vitro studies of its release into the extracellular space have shown that it is released from astroglial cells in several different ways. Activation of adenosine glutamate receptors is very rapid, occurring within 1 hour; there is stimulation of astroglial 5-hydroxytryptamine 1A (5-HT1A) receptors or a mediated release of adrenocorticotropic hormone

and corticotropin-like peptide. S100B can also be released from proliferating astrocytes.[28]

High levels of this protein in the CSF, which can be up to 40 times that of the serum, are generally associated with damage to the nervous system. Kinetic studies have shown that the half-life of S100B is approximately 1.5 h *in vivo*, for this reason, it has been accepted by some researchers as an early indicator of the function of the blood-brain barrier (BBB).[16] Extracellular high S100B concentrations have been associated with various neurological diseases such as Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, schizophrenia, epilepsy and TBI.[14,29]

### S100B and Epilepsy

In epilepsy, there is evidence indicating an increase in S100B levels, particularly after seizures. It has been reported that normal S100B levels attenuate epileptogenesis and that there is a relationship between high S100B concentrations and the severity of temporal lobe epilepsy (TLE). After surgical intervention in patients with refractory TLE, it has been reported that there was a threefold increase of S100B-immunoreactive astrocytes in neocortical sections, indicating a potential involvement of S100B in the pathophysiology of epilepsy.[30-32] Elevated S100B- levels have been demonstrated in adults and children with TLE. In one study, S100B was found to be higher in female TLE patients than in males, which was thought to indicate a possible interaction between S100B and sex hormones.[30,33] Khamis et al.[34] showed that S100B levels were higher in children with more severe epilepsy and structural changes on their MRI and were significantly increased in generalized epilepsy than in focal seizures. Therefore, they suggested that the observation of elevated S100B levels in children with epilepsy was associated with the presence and severity of brain damage of epileptic seizures.

In a randomized controlled study conducted by Maiti et al.[35] on 60 patients with focal seizures, it was determined that the S100B protein was significantly higher in epilepsy patients with focal seizures compared to normal individuals, and serum S100B values measured 2 and 4 weeks after starting antiepileptic therapy were found to be significantly lower. Moreover, it was determined that treatment with carbamazepine resulted in greater decrease in serum S100B levels compared to oxcarbazepine. It has been suggested that serum S100B can be used as a prognostic biomarker in focal seizures.[35,36] It has also been reported that long-lasting behavioral abnormalities with lithium-pilocarpine-induced SE during development in rats may be associated with elevated S100B levels in CSF.[37]

On the other hand, some studies do not support these findings. While studies have stated that there is no significant difference between epilepsy and control groups,[38,39] there are also studies reporting a decrease in serum S100B levels in epilepsy.[40,41] These stated that the short half-life (25-113 minutes) of S100B affected the reliability of the measurement. In their study on S100B, Atici et al.[42] also did not observe a significant increase in the sera of 39 pediatric patients with febrile convulsions compared to the control group.

However, out of the studies conducted so far, positive studies seem to predominate. Two recent large meta-analyses support-elevated levels of S100B protein in people with epilepsy.[8,21] In the detailed meta-analysis studies conducted by Simani et al.[36], 22 studies related to S100B were evaluated. In this study, it was established that S100B levels in patients with epilepsy were significantly increased compared to control group, which was consistent with other meta-analyses.

Experimental and clinical studies show that inflammation in the CNS is critical to epileptogenesis and induction of seizures. Neuroinflammation is thought to play a critical role in the pathogenesis of epilepsy. It contributes to disease progression, neurological comorbidities, frequency, and duration of seizures.[36,43] BBB dysfunction is thought to be triggered by neuroinflammation as inflammatory cytokines and other mediators affect the trans- and para-cellular pathways.[44] In addition, excessive epileptic discharge generation triggers BBB leakage and glial activation, which increases neuroinflammation. Thus, in epilepsy, there is a relationship between seizures and inflammation responsible for progression and tissue damage. Therefore, increased levels of brain biomarkers such as S100B could be indicative of BBB degradation and degree of neuroinflammation.[36]

## CONCLUSION

In conclusion, although the precise mechanisms underlying epilepsy pathogenesis are not fully understood, there is an increasing body of evidence suggesting that oxidative stress, dysfunction of the BBB, inflammation, and neuronal and glial damage contribute to the development of epilepsy disorders. The S100B protein has also been shown to increase in blood and CSF after these pathologies, especially after seizures. Thus, S100B can be considered as an important biomarker for epilepsy.

### Ethics

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: A.E.S., D.T.A., G.K., Design: A.E.S., D.T.A., G.K., Literature Search: A.E.S., Writing: A.E.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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