Review Article

S100B protein in serum is elevated after global cerebral ischemic injury

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BACKGROUND: S100B protein in patients with cardiac arrest, hemorrhagic shock and other causes of global cerebral ischemic injury will be dramatically increased. Ischemic brain injury may elevate the level of serum S100B protein and the severity of brain damage.

METHODS: This article is a critical and descriptive review on S100B protein in serum after ischemic brain injury. We searched Pubmed database with key words or terms such as "S100B protein", "cardiac arrest", "hemorrhagic shock" and "ischemia reperfusion injury" appeared in the last five years.

RESULTS: S100B protein in patients with cardiac arrest, hemorrhagic shock and other causes of ischemic brain injury will be dramatically increased. Ischemic brain injury elevated the level of serum S100B protein, and the severity of brain damage.

CONCLUSION: The level of S100B protein in serum is elevated after ischemic brain injury, but its mechanism is unclear.

KEY WORDS: S100B; Ischemic brain injury; Cardiac arrest; Hemorrhagic shock

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INTRODUCTION

S100B is a small calcium-binding protein in the neuronal system, and belongs to the S100 family. S100 proteins are a family of 25 homologous intracellular calcium-binding proteins characterized by EF hand motifs, low molecular weights (9–13 kDa), ability to form homodimers, heterodimers and oligomeric assemblies, and are characterized by tissue and cell-specific expression.[1] They are solely present in vertebrates. S100B protein is mainly expressed in the neuronal system such as astrocytes, maturing oligodendrocytes, dendritic cells, and Schwann cells. However, some other cells outside the brain, like kidney epithelial cells, ependymocytes, chondrocytes, adipocytes, and melanocytes, can also express S100B protein.[2,3]

S100B is glial-specific and is expressed primarily by astrocytes, but not all astrocytes express S100B. It has been shown that S100B is only expressed by a subtype of mature astrocytes that ensheath blood vessels and by NG2-expressing cells. Recent studies[4,5] have provided more detailed information about the mechanism (s) of action of S100B as an intracellular regulator and an extracellular signal. Intracellular S100B acts as a stimulator of cell proliferation and migration and an inhibitor of apoptosis and differentiation, which might have important implications during the development and repair of the brain, cartilage and skeletal muscle, the activation of astrocytes in the course of brain damage and neurodegenerative processes, and the remodeling of cardiomyocytes after infarction as well as in melanomagenesis and gliomagenesis.[6] As an extracellular factor, S100B engages receptor for advanced glycation end products (RAGE) in a variety of cell types with different outcomes (i.e. beneficial or detrimental, pro-proliferative or pro-differentiative) depending on the concentration attained by the protein, the cell type and the microenvironment.

S100B protein can be measured in both cerebrospinal

fluid and in blood serum. Wiesmann et al[6] reported that the median concentration in blood serum among healthy adults is about 50 ng/L. Some studies[7,8] confirmed that the low concentration (ng/L) of S100B protein has the function of nerve protective effect, but the high concentration (μg/L) of S100B protein has neurological toxicity.

Over the last decade, S100B has emerged as a candidate peripheral biomarker of blood brain barrier (BBB) permeability and central nervous system (CNS) injury. Elevated S100B levels accurately reflect the presence of neuropathological conditions including traumatic head injury or neurodegenerative diseases. S100B protein in the serum of patients with traumatic brain injury (TBI) will rise rapidly within 6 hours after injury. Studies[9,10] have proved that the higher level of S100B protein in serum, the more risks the patients with TBI. It is also reported that S100B protein could predict the prognosis of patients with TBI.[11,12]

Some recent studies, however, reported that S100B protein in patients with cardiac arrest (CA), hemorrhagic shock and other causes of global cerebral ischemic injury will be dramatically increased. This injury may elevate the concentration of serum S100B protein and the severity of brain damage.

METHODS

This article is a critical and descriptive review on S100B protein in serum after global cerebral ischemia injury. We searched Pubmed database with key words or terms such as "S100B protein", "cardiac arrest", "hemorrhagic shock" and "ischemia reperfusion injury" appeared in the last five years.

RESULTS

S100B protein and cardiac arrest

Cardiopulmonary resuscitation (CPR) is an emergency procedure, performed in an effort to manually preserve intact brain function until further measures are taken to restore spontaneous blood circulation and breathing in a person with CA.

Global cerebral ischemia can be caused by CA. The main purpose of cardiopulmonary resuscitation (CPR) for pre-hospital CA patients is to provide circulatory support, which could ensure the blood and oxygen supply for brain tissue. Sufficient blood supply to brain tissue will prevent irreversible brain damage caused by cerebral ischemia and hypoxia. The concentration of serum S100B protein is thought to be related to the survival rate of CA patients in hospitals,ie, the higher concentration of serum S100B protein in the patients,the lower survival rate the patients.[13]

The analysis[14] of serum S100B protein and neuron specific enolase (NSE) in CA patients found that S100B protein is superior to NSE in predicting neurological outcomes with CA patients. A study on S100B protein in CA patients within 24 hours after the restoration of spontaneous circulation (ROSC) also showed that the prognosis of neurological outcomes for such patients has a high sensitivity of 87% and a specificity of 100%.[15] This revealed the prognostic importance of S100B protein for CA. Meanwhile, CA patients show a good prognosis (a sensitivity of 70%, a specificity of 93%) when their concentration of serum S100B protein is less than 0.23 pg/mL. Moreover, they may acquire severe neurological defects and even be dead (a sensitivity of 83%, a specificity of 95%) when the concentration of serum S100B protein is higher than 1.64 pg/mL.[16]

There are two hypotheses that S100B protein in patient's serum increased after CA. First, CA may lead to inadequate blood flow perfusion for brain tissue which causes indirect brain damage.[17] Second, the injury of myocardial tissue caused by CA will release S100B protein, leading to the increase of this protein.[18] Researchers are in favor of the first hypothesis because the CNS is the major system generating and releasing the S100B protein *in vivo*. Furthermore, the limited content of S100B protein in myocardial cells indicates that S100B protein can not be a major factor.

S100B protein and acute hemorrhagic shock

Acute hemorrhagic shock could reduce tissue perfusion, resulting in the inadequate delivery of oxygen and nutrients that are necessary for cellular function, and also the destruction of the BBB.[19] The S100B protein located in the CNS can pass through the BBB and enter the peripheral blood circulation, thus elevating the content of serum S100B protein. A study[20] showed that the BBB is damaged when the content of serum S100B protein exceeded 0.027 ng/mL.

Pelinka et al[21] reported that the level of serum S100B protein will increase after hemorrhagic shock, and that this phenomenon is associated with the severity of shock but not the injury of peripheral soft tissue. Meybohm et al[22] also found that acute hemorrhagic shock could increase the level of serum S100B protein. Furthermore, when the cerebral perfusion pressure (CPP) of patients with hemorrhagic shock is less than 30 mmHg, S100B protein may be increased up to 0.75 μg/L or more. These findings illustrate that the decrease of CPP could

elevate the level of serum S100B protein.

Kang et al[23] found that critically ill patients without brain injury or mental disorder have a higher level of serum S100B protein, and the level is positively correlated with arterial blood lactate but negatively correlated with average arterial pressure and pH value of blood. Multiple regression analysis revealed that arterial blood lactate is an independent impact factor for the change of serum S100B protein. Also patients with a lower hemoglobin (Hb) level had a higher level of serum S100B protein than those with a higher Hb level. This indicates that the level of serum S100B protein may be related to the oxygen supply *in vivo*.

The above results indicate that serum S100B protein is increased after the decompensated stage of acute hemorrhagic shock, but the specific mechanism still needs further study. The reasons for the increase of serum S100B protein either because of hypovolemia, inadequate supply of oxygen for various tissues and organs, which leads to vascular endothelial cell injury[24] or myocardial cell damage or because of severe hypoxic-ischemic brain tissue that damaged the BBB, making S100B protein out of the CNS.

S100B protein and ischemic reperfusion injury

The change of serum S100B protein *in vivo* is not only related to acute cerebral ischemia, but also related to ischemia reperfusion injury (IRI). The level of serum S100B protein is increased after occurrence of acute stroke in patients. The reason is that the damage of astrocytes causes the extravasation of intracellular S100B protein. The level of serum S100B protein can reflect the severity of acute stroke and predict the prognosis of patients.[25] Moreover, systemic inflammatory response caused by acute ischemic stroke is independently associated with the level of serum S100B protein. This finding suggests that S100B protein plays an important role in inflammation response of the CNS.[26] Although the specificity of serum S100B protein is too low to diagnose acute stroke and the occurrence of its peak specificity is always late which means serum S100B protein is not suitable for the diagnosis of acute stroke, S100B protein is still regarded as a potential research area in acute ischemic stroke.[27]

A study[28] showed that the serum S100B protein *in vivo* with hemorrhagic shock significantly increased after fluid resuscitation. Serum S100B in a rat model with ligation of the carolid artery was increased over time, and serum S100B protein increased gradually with the time of the extension of cerebral ischemia reperfusion.[29] This indicated that following the extension of the time with reperfusion, the damage to the brain tissue will increase gradually.

When fluid resuscitation works after hemorrhagic shock, ischemia reperfusion could affect other organs such as the liver, kidneys and intestine. In a model of ischemia reperfusion, the level of S100B protein was increased significantly after three hours of reperfusion.[28] Thus it is not clear that whether the ischemia reperfusion model caused by ligation of the carotid artery has the same impact as the cerebral ischemia reperfusion model caused by systemic blood loss.

CONCLUSIONS

As an important serological marker of the CNS, S100B protein is important for determining the prognosis of patients with TBI. The sensitivity for determining the prognosis of patients with TBI through serum S100B protein is 80%; however, the specificity is too low and its impact is vulnerable to the tissues outside the brain.[30] Even ischemia reperfusion reaction in the liver, kidney, and intestine can also affect the S100B levels in serum.[28] The level of serum S100B protein will rise after acute massive blood loss leading to hemorrhagic shock *in vivo*, and this upward trend is associated with the severity of shock. The increase of S100B protein may be due to the damaged BBB followed by low CPP released S100B protein into the peripheral blood from the brain tissue. S100B protein released into the extracellular regulator showed different physiological and pathological effects according to its own concentration. However, the specific mechanism of action of S100B protein in patients with ischemic brain injury is still rarely reported.

Although current studies have confirmed that hemorrhagic shock can promote the release of S100B protein from the CNS, it is not clear that which cells in the brain tissue secrete and release S100B protein as well as the impact of S100B protein released in the extracellular regulator after hemorrhagic shock. Fluid resuscitation is an important treatment for hemorrhagic shock, and the specific mechanism of S100B protein acts in ischemia reperfusion injury in brain tissue is not yet clear. Future research should focus on the following aspects: the specific mechanisms of the secretion and release of S100B protein from brain tissue after acute hemorrhagic shock; the specific functional role of S100B protein in acute hemorrhagic shock; the interactions between serum S100B protein and ischemia reperfusion injury after fluid resuscitation with acute hemorrhagic shock.

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REFERENCES

1 Santamaria-Kisiel L, Rintala-Dempsey A, Shaw G. Calcium-dependent and -independent interactions of the S100 protein family. Biochem J 2006; 396: 201–214.
2 Donato R, Sorci G, Riuzzi F, Arcuri C, Bianchi R, Brozzi F, et al. S100B's double life: intracellular regulator and extracellular signal. Biochim Biophys Acta 2009; 6: 1008–1022.
3 Huang M, Dong XQ, Hu YY, Yu WH, Zhang ZY. High S100B levels in cerebrospinal fluid and peripheral blood of patients with acute basal ganglial hemorrhage are associated with poor outcome. World J Emerg Med 2010; 1: 22–31.
4 Bianchi R, Adami C, Giambanco I, Donato R. S100B binding to RAGE in microglia stimulates COX-2 expression. J Leukoc Biol 2007; 81: 108–118.
5 Bianchi R, Giambanco I, Donato R. S100B/RAGE-dependent activation of microglia via NF-[kappa] B and AP-1 Co-regulation of COX-2 expression by S100B, IL-1 [beta] and TNF-[alpha]. Neurobiol Aging 2010; 31: 665–677.
6 Wiesmann M, Missler U, Gottmann D, Gehring S. Plasma S-100b protein concentration in healthy adults is age-and sex-independent. Clin Chem 1998; 44: 1056–1058.
7 Mori T, Koyama N, Arendash GW, Horikoshi-Sakuraba Y, Tan J, Town T. Overexpression of human S100B exacerbates cerebral amyloidosis and gliosis in the Tg2576 mouse model of Alzheimer's disease. Glia 2010; 58: 300–314.
8 Villarreal A, Aviles Reyes RX, Angelo MF, Reines AG, Ramos AJ. S100B alters neuronal survival and dendrite extension via RAGE-mediated NF-kappaB signaling. J Neurochem 2011; 117: 321–332.
9 Vos PE, Jacobs B, Andriessen TM, Lamers KJ, Borm GF, Beems T, et al. GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology 2010; 75: 1786–1793.
10 Bloomfield SM, McKinney J, Smith L, Brisman J. Reliability of S100B in predicting severity of central nervous system injury. Neurocrit Care 2007; 6: 121–138.
11 Wiesmann M, Steinmeier E, Magerkurth O, Linn J, Gottmann D, Missler U. Outcome prediction in traumatic brain injury: comparison of neurological status, CT findings, and blood levels of S100B and GFAP. Acta Neurologica Scandinavica 2010; 121: 178–185.
12 Unden J, Romner B. Can low serum levels of S100B predict normal CT findings after minor head injury in adults?: An evidence-based review and meta-analysis. J Head Trauma Rehabil 2010; 25: 228–240.
13 Song KJ, Shin SD, Ong ME, Jeong JS. Can early serum levels of S100B protein predict the prognosis of patients with out-of-hospital cardiac arrest?. Resuscitation 2010; 81: 337–342.
14 Shinozaki K, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Abe R, et al. S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review. Crit Care 2009; 13: R121.
15 Mörtberg E, Zetterberg H, Nordmark J, Blennow K, Rosengren L, Rubertsson S. S-100B is superior to NSE, BDNF and GFAP in predicting outcome of resuscitation from cardiac arrest with hypothermia treatment. Resuscitation 2011; 82: 26–31.
16 Helánová K, Pařenica J, Jarkovský J, Dostálová L, Littnerová S, Klabenešová I, et al. S-100B protein elevation in patients with the acute coronary syndrome after resuscitation is a predictor of adverse neurological prognosis. Vnitr Lek 2012; 58: 266–272.
17 Lippi G, Aloe R, Numeroso F, Cervellin G. The significance of protein S-100B testing in cardiac arrest patients. Clin Biochem 2011; 44: 567–575.
18 Wang XJ, Wang M. The S100 protein family and its application in cardiac diseases. World J Emerg Med 2010; 1: 165–168.
19 Krizbai IA, Lenzser G, Szatmari E, Farkas AE, Wilhelm I, Fekete Z, et al. Blood-brain barrier changes during compensated and decompensated hemorrhagic shock. Shock 2005; 24: 428–433.
20 Blyth BJ, Farhavar A, Gee C, Hawthorn B, He H, Nayak A, et al. Validation of serum markers for blood-brain barrier disruption in traumatic brain. J Neurotrauma 2009; 26: 1497–1507.
21 Pelinka LE, Bahrami S, Szalay L, Umar F, Redl H. Hemorrhagic shock induces an S 100 B increase associated with shock severity. Shock 2003; 19: 422–426.
22 Meybohm P, Cavus E, Dörges V, Weber B, Stadlbauer KH, Wenzel V, et al. Release of protein S100B in haemorrhagic shock: effects of small volume. Resuscitation 2008; 76: 449–456.
23 Kang J, Gong P, Ren YB, Gao DN, Ding QL. Effect of β-sodium aescinate on hypoxia-inducible factor-1α expression in rat brain cortex after cardiopulmonary resuscitation. World J Emerg Med 2013; 4: 63–68.
24 Elmer J, Alam H, Wilcox SR. Hemoglobin-based oxygen carriers for hemorrhagic shock. Resuscitation 2011; 83: 285–292.
25 James ML, Blessing R, Phillips-Bute BG, Bennett E, Laskowitz DT. S100B and brain natriuretic peptide predict functional neurological outcome after intracerebral haemorrhage. Biomarkers 2009; 14: 388–394.
26 Beer C, Blacker D, Bynevelt M, Hankey GJ, Puddey IB. Systemic markers of inflammation are independently associated with S100B concentration: results of an observational study in subjects with acute ischaemic stroke. J Neuroinflammation 2010; 7: 71.
27 Dassan P, Keir G, Brown MM. Criteria for a clinically informative serum biomarker in acute ischaemic stroke: a review of S100B. Cerebrovasc Dis 2009; 27: 295–302.
28 Pelinka LE, Harada N, Szalay L, Jafarmadar M, Redl H, Bahrami S. Release of S100B differs during ischemia and reperfusion of the liver, the gut and the kidney in rats. Shock 2004; 21: 72–76.
29 Ohtani R, Tomimoto H, Wakita H, Kitaguchi H, Nakaji K, Takahashi R. Expression of S100 protein and protective effect of arundic acid on the rat brain in chronic cerebral hypoperfusion. Brain Res 2007; 2: 195–200.
30 Rainey T, Lesko M, Sacho R, Lecky F, Childs C. Predicting outcome after severe traumatic brain injury using the serum S100B biomarker: results using a single (24 h) time-point. Resuscitation 2009; 80: 341–345.

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