REVIEW ARTICLE

Targeting S100B Protein as a Surrogate Biomarker and its Role in Various Neurological Disorders

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Abstract: Neurological disorders (ND) are the central nervous system (CNS) related complications originated by enhanced oxidative stress, mitochondrial failure and overexpression of proteins like S100B. S100B is a helix-loop-helix protein with the calcium-binding domain associated with various neurological disorders through activation of the MAPK pathway, increased NF-kB expression resulting in cell survival, proliferation and gene up-regulation. S100B protein plays a crucial role in Alzheimer's disease, Parkinson's disease, multiple sclerosis, Schizophrenia and epilepsy because the high expression of this protein directly targets astrocytes and promotes neuroinflammation. Under stressful conditions, S100B produces toxic effects mediated through receptor for advanced glycation end products (AGE) binding. S100B also mediates neuroprotection, minimizes microgliosis and reduces the expression of tumor necrosis factor (TNF-alpha) but that are concentration-dependent mechanisms. Increased level of S100B is useful for assessing the release of inflammatory markers, nitric oxide and excitotoxicity dependent neuronal loss. The present review summarizes the role of S100B in various neurological disorders and potential therapeutic measures to reduce the prevalence of neurological disorders.

1. INTRODUCTION

Neurodegenerative disorders are characterized by selective dysfunction and gradual loss of neuronal populations associated with pathologically altered protein that mainly deposits in the brain and spinal cord [1]. The deposition of extracellular and intracellular proteins fibrils, oxidative stress, and mitochondria dysfunction are the key pathological features of many different neurological disorders. Oxidative stress is indicated by over-production of reactive oxygen species (ROS) that can cause mitochondrial DNA mutations, destroy the respiratory chain, alter the permeability of the membrane and affect calcium homeostasis and mitochondrial protection systems [2]. During normal physiological conditions, 1–5% of O_2 is transformed to ROS, thus most estimates have suggested that the majority of intracellular ROS are produced from mitochondria. Mitochondrial superoxide radicals are produced primarily in the electron-transport chain (ETC), namely complex I and II. Complex III is the main site of ROS production under normal metabolic conditions, and due to this, the free radical can attack directly the respiratory chain of the mitochondria [3]. When free radicals attack mitochondrial DNA, it can amplify oxidative stress by reducing the expression of critical proteins that are important for electron transport; this results in a vicious cycle of

ROS and organ dysregulation that ultimately triggers apoptosis [4]. Furthermore, the ETC is especially prone to both NO- and ONOO-mediated damage. Oxidation and nitration of protein in the ETC result in altered function of many metabolic enzymes [5]. Chronic exposure to ROS may result in oxidative damage to mitochondrial and different cellular proteins, nucleic acids, and lipids, and acute exposure to ROS may inactivate complexes I, II, and III, leading to the shut-down of mitochondrial energy production which leads to death of neurons [6].

Nitric oxide (NO) is a key secondary cellular transporter which at nanomolar concentration inhibits the cytochrome oxidase (complex IV) enzyme activity, impairs mitochondrial metabolism and contributes to free radical formation. NO reacts with these negatively charged anion particles to form peroxynitrite, which is a more harmful cytotoxic agent than NO and a mediator of vascular tissue damage and a cause of the death of neurons. In past decades, these free charged particles have strongly been linked with neurological disorders like Alzheimer's disease (AD) [7]. Around, 90%-95% of the overall production of adenosine triphosphate (ATP) among aerobic cells needs oxygen. ATP synthesis *via* the respiratory chain of mitochondria is the outcome of electron transport across the ETC coupling oxidative phosphorylation melatonin, mitochondria, and cellular bioenergetics [8]. The produced superoxide ions are neutralized by the intra-mitochondrial redox systems that resist oxidative damage and, improve ATP production. Damaged mitochondria in aging and neurodegenerative diseases are not capable of

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meeting required energy demand and ultimately render deaths of neuronal cells. The large amount of NO which is released from glial cells through the expression of iNOS after their stimulation is neurotoxic because it induces oxidative stress, excitotoxicity and mitochondrial dysfunction [9]. In one of the reported study when old rats' brain mitochondria were compared with those of young rats', significant endogenously decreased antioxidants and superoxide dismutase activity were found, due to excessive oxidative injury to proteins and lipids and lower mitochondrial complex I, IV and V activities. The NO is a multi-target inhibitor of mitochondrial oxidative phosphorylation and more prominently inhibits complex I and II [10].

The S100B protein belongs to the mutagenic family with 25 members (like calmodulin/ parvalbumin/ troponin C) and was named because of its solubility in 100% saturated solution of ammonium sulfate at neutral pH. The first member of this family was the unfractionated mixture of two proteins S100A1 and S100B [11-13]. Structurally, S100B protein consists of two alpha helix-loop-helix calcium-binding proteins involved in cytoskeleton formation and cellular proliferation [14]. The other members of S100B protein like S100A1, S100A8 help to control multi-cellular functions like cell-cell communication, cell growth and cardiac muscle contraction by calcium-induced calcium release (CICR) cascade [15]. The intracellular signaling of these proteins is initiated by extracellular stimuli *via* interacting with different cellular proteins known as target proteins [16].

Persistent receptor for advanced glycation end product (RAGE) activation by S100B at micromolar concentration produces oxygen radical in high amounts that lead to mitochondrial dysfunction and apoptosis. Moreover, this concentration was reported for iNOS up-regulation to induce the release of NO and NO-dependent neuronal and glia death, facilitating glutamate-mediated death of neurons, upregulation of COX-II expression in microglia, increasing ROS production in neurons and arrest of the cell cycle [17]. In rats, iNOS is stimulated by S100B primarily in cortical astrocytes *via* the pathway of signal transduction involving transcription factor NF-kB activation. The activation of NF-kB was confirmed by p65 NF-kB subunit translocation, NF-kB transcriptional activity stimulation [18]. Furthermore, oxidative stress due to ROS production induces mutations of the mitochondrial DNA, dysfunction of the respiratory system of mitochondria, membrane permeability alterations and affects calcium balance and mitochondria defensive system. All mentioned alterations lead to development of neurodegenerative diseases, such as AD, PD and ALS [5].

The scientist has reported that S100B protein controls the activation of Glial fibrillary acidic protein (GFAP), polymerization of tubulin and DNA repair [19]. GFAP is a characteristic intermediate filament (IF) protein in astrocytes which are a type of macroglial cells in the CNS that control brain homeostasis in the healthy and disease state. Astrocytes are supposed to be a reactive phenotype in acute CNS trauma, ischemia and neurodegenerative disorders. These astrocytes activate cell protection which induces chemotaxis,

pro-inflammatory cytokines release through NF-kβ and p38 MAPK signaling [20].

Brandt *et al.* in 2017 demonstrated that the microtubule dysfunction relates some of the degenerative events like synaptic impairment associated with loss of dendritic spines, dendritic simplification that associates with the extend of microtubule stability and cell death that provides a useful target to prevent several degeneration processes in AD [21]. Microtubule-associated tau protein plays an important role in stabilizing microtubule assembly and cellular morphology. In AD, hyperphosphorylated tau proteins are aggregated into paired helical filaments and accumulated in the neurons with the formation of neurofibrillary tangles. Any imbalance in the regulation of S100B protein, kinases and protein phosphatases is the direct cause of tau hyperphosphorylation [22]. So, the inhibitor of S100B protein or its down-regulation may be useful to prevent tauopathy in AD. The release of S100B protein in the body is controlled by metabolic stress like hypoxia or glucose deprivationduring the developmental stage of the astrocytes. The release is stimulated in response to external stimuli like 5HT, glutamate, pro-inflammatory cytokines (IL-1 beta and TNF-alpha), β-amyloid peptides, lysophosphatidic acid, natural plant antioxidants (epicatechin and resveratrol) and by increased calcium concentration [23].

In PD, an increase in caspase-3 expression and activation of iNOS result in dopaminergic cell death and production of apoptotic bodies [24, 25]. Similarly, nitric oxide released by S100B causes astrocytes to undergo apoptotic cell death [26]. During the course of disease, S100B, alpha-beta, AGEs and RAGE ligands like TRR, HMGB1, S100A6, S100A8/A9 and S100A12 start to accumulate in the neuronal cell, more prevalent in the dopaminergic cell. S100B secretion and chronic activation of RAGE associated with neuropathological markers like microglia activation ROS, NFT formation, neurite degeneration and neuronal apoptosis lead to cognitive impairment [27]. In schizophrenia, S100B after release from glial cells, NK cells and CD8+ lymphocytes enhances the cytokines level and is a proposed marker of glial cell dysfunctioning. Furthermore, S100B also shows adipokine like properties and may get unbalanced in schizophrenia due to disturbed insulin signaling which also releases free fatty acids from adipose tissue [28].

The expression of S100B is affected by aging. In the available literature, the researcher has found age-related changes in S100β expression in different species. Some authors have suggested an increase in the expression of S100β in the brain cortex and hippocampus by activating astrocytes with age [29]. The post-mortem study has shown that number of S100B-positive cells and tissue which consist of S100B mRNA and S100B protein were increased with advancing age. In the case of overexpression of S100β, the protein enhances the production of proinflammatory cytokines, which has a detrimental impact and contributes to neurons and glial cells apoptosis [30]. In addition, the hippocampus is particularly vulnerable to aging, which can contribute to the spatial learning disorder, whereas other brain regions,

like PAG, can function properly. These neurological disorders are possibly induced by $Ca2^+$ dependent processes, which influence long-term depression (LTD) and long-term potentiation (LTP) [31]. In patients with AD, the presence of highly reactive astrocytes surrounding neuritic plaques has been observed in the temporal lobe. This protein also had an increased reactivity in patients with the Down syndrome [32]. In cortex and hippocampus parts of the brain, the age and sex-related changes in S100β expression have been observed. Studies have shown that in female rats at the beginning of the rest phase of the regular process, the maximum expression of S100β was observed, while in male rats, it was observed at the beginning of the motor activity phase [33]. Older rats have increased protein expression compared with young rats. Moreover, significant differences of S100β have been observed within the differences in the region of the brain in rats. Some report has found that SAMP mice have increased S100B in the hippocampus and cerebral cortex compared to control mice [34]. The conclusion of available data has explained that the expression of S100B is affected by aging.

Apart from S100B, other calcium-binding proteins (CaBPs) members of the EF-hand family are parvalbumin, calretinin and calbindin, whose functions in neurons are unknown. But these proteins have a great interest in neuroanatomy and neuropathology since immunocytochemistry for parvalbumin, calretinin and calbindin has shown to be helpful for characterizing chemically and morphologically sub-populations of neurons in the nervous system [35]. Various reports have explained that CaBPs are involved in numerous activities, including cell signalling, calcium uptake and transportation, cell motility and intracellular acceptance. Recent experiments have shown that intracellular CaBPs are important methods in central and peripheral nervous systems for investigating neuronal typology [36]. These proteins contain various EF-hand domains in which parvalbumin contains 3 domains and calretinin and calbindin both contain 6 domains with the binding of 3, 5 and 4 ions of calcium, respectively [37]. All three of these CaBPs have a strong calcium-binding ability, although their kinetics seems to vary, for example, slow-binding kinetics is reported in parvalbumin condition. Various neuronal sub-populations are reported for expressing these CaBPs. Majorly, immunoreactive cells of these proteins are smooth non-pyramidal interneurons and take part in various multifaceted cortical circuits that may vary depending upon cortical area, species or on the layer where they locate [38]. In neocortical interneurons, inhibitory neurotransmitter GABA is co-localized with these three CaBPs along with nitric oxide synthase and neuropeptides [39]. Among GABAergic interneurons, are parvalbumin expressed by hippocampal and cortex basket cells, cerebellum purkinje cells, calbindin expressed by purkinje cells of cerebellar, sub-population of hippocampus [35, 40] and outward CA1 pyramidal neurons [41], also cortical populations. The calretinin was found initially in the retina, cortex interneurons [42] and also in the hippocampus along with granule cells in cerebellar [33]. It was observed that neurons that are expressing specific CaBPs could be more susceptible to neu-

rodegeneration. The effect of CaBPs expression on neuronal susceptibility tends to be highly dependent on the disease or experimental disease model, where the severity of the brain injury, and also the specific calcium elevation pathway can play an important role [35, 43]. There are also many other factors involved in assessing the sensitivity of different neurons to degeneration, including, their circuit communication, trophic support network, relative synaptic inputs to extra-synaptic NMDA receptors, as well as their energy needs [40]. High expression of CaBPs is associated with high calcium influx rates and intracellular release. These same neurons could also be the most risk of degeneration due to the demands of high energy. Furthermore, understanding of the factors regulating CaBPs expression and how neurons regulate this under pathophysiological conditions could be allowed for the development of neuroprotective strategies [40].

2. STRUCTURE OF THE S100B PROTEIN

S100B is zinc (Zn^{2+}) and calcium (Ca^{2+}) binding acidic protein confined to nucleus and cytoplasm of a broad range of cells. S100 protein genes comprise 13 members present as a cluster on chromosome 1q21 [45, 46]. Structurally, it contains two binding regions of EF-hand type, known as a helix-loop-helix motif joined by a central hinge region [27]. The protein is composed of 2 identical chains of the 91-amino acid polypeptide which further contains two proposed EF-hands that are helix-loop-helix calcium-binding regions. Every subunit of S100B incorporates four helixes (helix 1, E2-R20; helix 2, K29-N38; helix 3, Q50-D61; and helix 4, F70-A83) and one antiparallel beta-sheet (strand 1, K26-K28; and strand 2, E67-D69). These helices and sheets form normal and pseudo-EF-hands jointly [47, 48]. The C-terminal domain contains canonical 12 amino acid-binding loops with classical EF-hand and the N-terminal domain containing the 14 S100B specific amino acid–binding loops [49, 50]. The amino acid sequence has been found to have areas of an intense grouping of lipophilic, basic and acidic amino acids and having a calcium-binding region in the acidic portion [51]. S100b with a moderate affinity (2-20M) binds with two calcium ions per subunit [27] (Fig. **1**).

Moreover, calcium-binding to EF-hand initiates structural changes that permit the target proteins interactions. S100B proteins are differentiated from other helix-loop-helix EF-hand proteins by their distinct ability to bind Ca^{2+} ions in their amino-terminal binding sites which is a peculiar diametric building design. Moreover, there is a potential of transition metal binding such as copper, zinc and manganese at dimer interface at histidine-rich binding sites [27]. In the existence of magnesium and potassium, the affinity of the protein for Ca^{2+} ions is decreased. The calcium-binding occurs possibly at two sites that are alpha and beta, which is strongly antagonized by potassium [52]. This protein interacts with the target proteins shown to bring in cysteine residues (one on S100A1 and two in S100B); moreover at a stretch of 13 amino acids, a linker region in the middle joins two EF-hand calcium-binding domains [53].
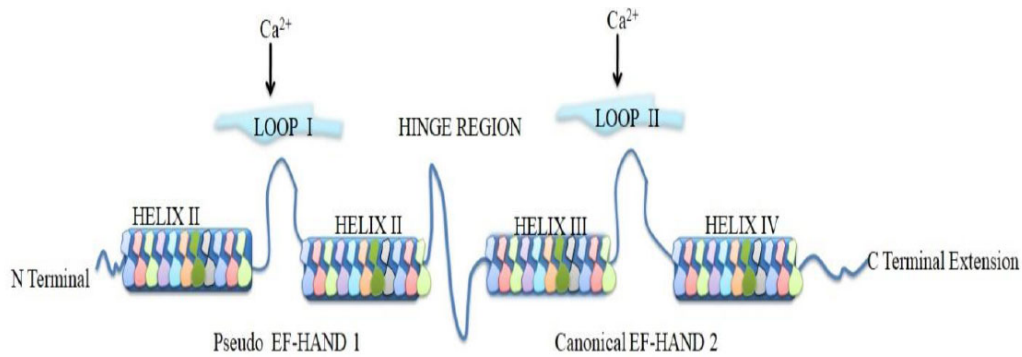
Fig. (1). Structure of S100B protein. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*
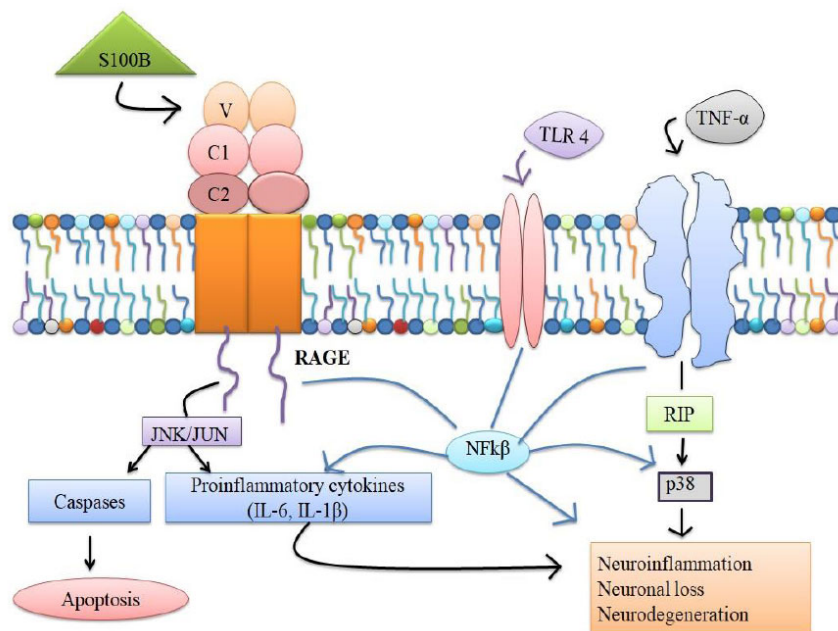

Fig. (2). Overactivation of S100B protein increase proinflammatory markers release and neurodegeneration. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3. THE RECEPTOR OF S100B PROTEIN

S100 proteins act on RAGE and TLR-4 receptors. RAGE is a cell surface receptor of immunoglobulin present on various cell types like mononuclear phagocytes, tissue macrophages, cardiac myocytes, lungs, fibroblasts, epithelial cells, endothelial cells, neurons and smooth muscle cells [54]. They are also described as a pattern recognition receptor. The activation of extracellular RAGE domains by S100 proteins initiates multiple intracellular signaling pathways and various transcription factors such as NF-kB, AP-1 and STAT$_3$ (Signal transducer and activator of transcription 3), that leads to increased expression of proinflammatory cytokines and cellular adhesion molecules. S100 proteins interfere with diverse RAGE domains such as V domain, C1 domain and C2 domain [55]. The V domain is located at N-terminal at most lateral position from the plasma membrane, whereas the C2 domain is located near to the membrane. The two adjacent domains V and C1 join together and build a little bent elongated structure [56, 57] (Fig. **2**).

S100B protein interferes with the V domain whereas other proteins like S100A12 and S100A6 are known to interact with V and C domain. S100A12 interacts *via* V and C1 domain and S100A6 interacts *via* V and C2 domain. The exact binding site of S100A8/A9 in the RAGE domain has not been confirmed yet. The RAGE domain is mainly activated by different S100 proteins such as S100B, S100A12, S100A8/A9, etc., and further they can lead to the MAPK pathway activation and NF-Kb translocation from the cytosol to the nucleus, which results in the cell survival and proliferation as well as gene upregulation [55].

4. S100B IN ALZHEIMER`S DISEASE

AD is an irreversible, progressive neurodegenerative disorder that slowly shatters thinking, memory ability and the potential to carry out easy tasks [58]. The initial histopathological markers of AD are neurofibrillary tangles found intracellularly and amyloid plaques found extracellularly that are well known to degenerate hippocampal neurons [59]. In AD patients, the level of S100B protein in frontotemporal lobe promotes inflammatory cascade, oxidative stress and alters Ca^{2+}homeostasis [60]. Oxidative stress initiates mitochondrial DNA damage, leading to the propagation and/or destruction of neurons, which has been concerned in the pathogenesis of neurological disorders. Various reports have hypothesized that an imbalance between highly cytotoxic $ONOO-$ and protective NO could be crucial for several vascular and neuronal diseases including AD [5]. The production NO occurs due to the increase in the production of Aβ either through disruption of Ca^+ homeostasis and subsequent increase in intracellular Ca^+ (eNOS and nNOS mediated NO release) or through interactions with glial cells (iNOS-mediated NO release) [61]. NO is a free radical with the potential to produce peroxynitrite. These ROS induce various mechanisms of neurotoxicity, including alteration of protein/DNA, mitochondria dysfunction, lipid peroxidation, neuro-inflammation, and apoptosis, inducing integrity of cellular membrane, which leads to further Ca^+ influx and NO release [62]. These mechanisms are known to be implicated in cell death and observed cognitive impairments in AD [63].

There is a distinct interaction between extracellular beta-amyloid and S100B protein expression which is chronically elevated in AD and is associated with senile plaques. This biomarker may play roles in amyloid aggregation and is helpful to determine brain distress [64]. Activated astrocytes are well-recognized components of Aβ plaques in AD. These activated astrocytes found in the AD patient brain markedly over-express S100B which is reflected by its increased brain tissue level. Most of these activated astrocytes and S100B overexpression in the brain of AD patients are closely associated with either diffuse or neuritic Aβ plaques. Distribution of these astrocytes across brain regions recognized distribution patterns for Aβ plaques. These topographical associations between S100B overexpression activated astrocytes and Aβ plaques in AD together with the known neurotrophic effects of S100B suggest that S100B overexpression may be an important pathogenic factor responsible for genesis and evolution of neuritic plaques in AD. Astrocytes activation and overexpression of S100B are prominent and consistent features of AD conditions that confer increased risk for AD. S100B has both trophic and potentially toxic effects on neurons and neurites which suggests that S100B overexpression plays an important role in the genesis of neuritic changes in Aβ plaques. In the late AD stage, the progression of non-fibrillary amyloid deposits as neurite forms consequently leads to the progression of the disease itself [65].

It has been evidenced that the synthesis of both S100B protein mRNA and S100B protein in the culture of astrocytes is stimulated by beta-amyloid [14]. The accumulation and influx of alpha-beta (α-β) in the brain are mediated by RAGE. Directly or indirectly α-β initiates calcium homeostasis dysregulation which leads to activation of S100B protein. Glial cells activation by RAGE leads to NF-kB beta activation that causes gene transcription and inflammatory cytokines release [66]. In AD patients, brain is the intense site of inflammation and oxidative stress that brings about AGEs formation. S100B protein, alpha beta, AGEs and other RAGE ligands as HMGB1, TTR, S100A6, S100A8/A9 and S100A12 concentrate in the brain during the disease course. Excessive release of S100B and RAGE also initiates neuropathological changes in the brain through activation of microglia, neurite degeneration, neuronal apoptosis and formation of NFT that finally leads to impairment of memory [27].

Excessive AGE formation by protein modification also triggers RAGE dependent oxidative stress and NF-kβ. The activated NF-kB leads to the elevated expression of RAGE because of the NF-kB response element present within the RAGE promoter region [65]. Activation of both RAGE and NF-kB leads to alteration in neuronal redox potential and neuroinflammation. At the site of inflammation, high levels of AGEs, NFT and senile plaques are localized in the brain of AD patients [67]. Amyloid-forming proteins as amyloid-beta peptides and TTR initiate the formation of the second group of RAGE ligands. The APP processing by beta and gamma secretase leads to amyloid beta-peptide production. Accumulated amyloid beta proteins in the AD patient brain play an important role in disease pathogenesis. The transport of amyloid beta through the cell membrane of neurons and BBB is also evidenced to be mediated by RAGE. Furthermore, in AD patients, TTR is shown to have a protective effect by binding to amyloid beta in a chaperone-like manner [55].

5. S100B IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a prevalent progressive neurodegenerative disorder that is described by aggregation of α-synuclein in cortical or brain stem region [68]. The first and most prominent physical disabilities due to these variations include motor incoordination that is collectively called Parkinsonism. These include insufficiency and slow movement that is akinesia, bradykinesia, rigidity and tremors produced at rest [69]. Pathogenesis of PD focuses on ROS, the initiation of oxidative stress that results in oxidative damage to substantia nigra pars compacta. Free radical species being the cause of the death of a dopaminergic cell in PD is unclear, but some data have suggested that hydroxyl radical (O-H') , NO, and peroxynitrite are involved [70]. Nitric oxide synthase (NOS) activation produces NO, which reacts with superoxide to form peroxynitrite. This molecule modifies nucleic acid, protein, and lipid, in an oxidative manner, resulting in nuclear damage, proteasome inhibition, mitochondrial damage and endoplasmic reticulum stress (ER). Excessive level of nitrosative stress leads to the hyperactivation of glutamate receptor group N-methyl-D-aspartate (NMDA), mitochondrial dysfunction and cell aging. Excessive free radicals and NO species were reported to activate the pathological

mechanism including abnormal mitochondrial dynamics, misfolded proteins, and apoptotic pathways in dopaminergic cells [71]. Some studies have suggested that excessive production of NO may contribute to these pathological processes, mainly by S-nitrosylation of specific target protein, such as ubiquitin-protein ligase, parkin, protein disulfide isomerases (PDI), and mitochondrial degradation by ß-amyloid-related S-nitrosylation of dynamin-related protein-1. PDI is responsible for the normal folding of proteins in the ER, among these proteins [72]. In addition, No mediated effects on dopaminergic neuron cells can include the inhibition of mitochondria complexes I, II, and IV, cytochrome oxidase, ribonucleotide reductase, glyceraldehyde-3-phosphate dehydrogenase, superoxide dismutase, lipid peroxidation, activation or initiation of DNA strand breakage, protein oxidation and increased production of toxic free radicals including hydroxyl radicals and peroxynitrite. Evidences have suggested that excessive RNS/ROS may lead to UPS impairment and misfolding of protein molecules, resulting in aggregation of protein and dopaminergic neuronal death [73].

The low expression S100B protein results in neuroprotection due to decreased microgliosis, AGEs and TNF-alpha expression. There are increased indications that S100B is not only involved in inflammation but also in neurodegenerative disease, activates proinflammatory cytokine release and leads to damage to dopaminergic neurons. The increased level of S100B proteins in post-mortem substantia nigra of PD patients has been reported as compared with normal tissue

group in the CSF [74]. Furthermore, S100B shows dual action at low concentration (nanomolar), activates neurotrophic factor and promotes neuronal survival as well as the growth of neurite during the development phase [75]. It also initiates neuronal apoptosis at micromolar concentrations both by direct action on neurons and microglia activation [76]. To some range, these effects may be mediated by an iNOS enzyme which increases nitric oxide production, intracellular calcium levels and activation of caspase-3 [24]. Further, it has been reported that the treatment of astrocytes culture with S100B protein leads to iNOS activation and nitric oxide production. Nitric oxide produced in response to S100B can cause astrocytes to undergo apoptotic cell death. Nitric oxide mediated excitotoxicity, inflammation, oxidative stress, mitochondrial function impairment, DNA damage and S-nitrosylation of various proteins lead finally to neuronal death [47] (Fig. **3**). This indicates that S100B could be a promising marker for the degree of disease severity during the beginning of the disease. The PD patients have lower levels of S100B and individuals with reduced S100B levels could be more vulnerable to neurological problems. These findings suggest that S100B may have a possible role in either the underlying PD development mechanism or in the assessment of disease [14] Furthermore, astroglial C6 and oligodendroglial OLN-93 cells treatment with haloperidol and clozapine at a concentration corresponding to the therapeutic dose range of these drugs decreases the S100B release *in vitro* [77].
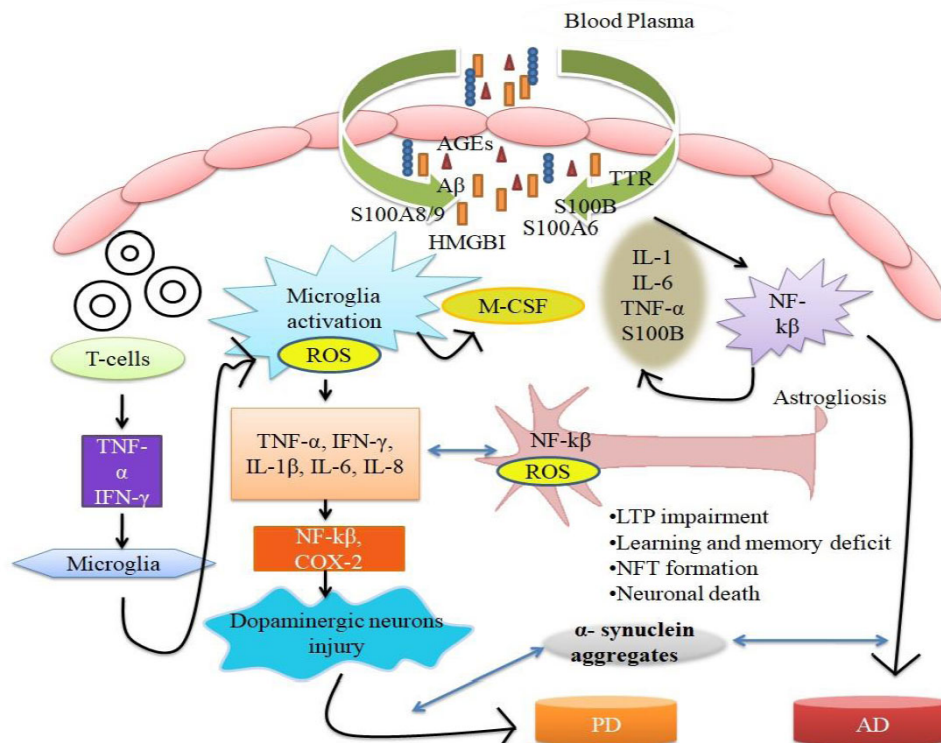

Fig. (3). S100B protein role in Parkinson's and Alzheimer's disease. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

6. S100B IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease of CNS caused by chronic inflammatory demyelination of neurons, affecting young people [78]. In early disease stages, it is characterized by the T-cells activation, infiltration and accumulation of monocytes derived macrophages that promote damage to myelin sheath which further leads to the formation of focal demyelinated lesions [79]. Moreover, a higher S100B level triggers the activation of astrocyte and microglial promoting the NO release [80]. NO is a free radical that is found at a higher concentration than the normal in inflammatory lesions of MS. This increased concentration occurs because of the appearance of iNOS in astrocytes and macrophages. In fact markers of NO production such as nitrite and nitrate concentrations are increased in the blood, CSF and urine of MS patients. Also, evidences suggest the function of NO in various disease features such as BBB damage, injury of oligodendrocyte, demyelination and degeneration of axon and it further contributes to functional loss due to axonal conduction impairment [81].

Elevated S100B level was firstly detected in the cerebrospinal fluid of acute-phase MS patients [82]. In the diagnosis of relapsing-remitting MS patients, elevated levels of S100B in the CSF or serum were detected, which decreased after therapy with immunosuppressive or natalizumab [83]. During the injury, an increased level of S100B may induce glial reactivity, aggravating tissue damage or delaying remyelination. Increased S100B levels were detected in the CSF of relapsing-remitting MS patients after diagnosis [84]. Active demyelinating MS lesions showed an elevated level of S100B and its receptor, RAGE in the lesion area while chronic active lesions showed raised S100B level in demyelinated areas with lower expression of RAGE receptor in the rim [85].

Interestingly, reactive astrocytes were recognized as the prevailing S100B cellular source, although activated microglia or macrophages express RAGE. A study on the expression of RAGE and S100B in MS lesions reveals that active demyelinating lesions in MS are characterized by myelin loss and increased level of proteolipid protein positive macrophages (PLP). In white matter regions, S100B expression was markedly increased and localized to cell bodies and reactive astrocytes like cell processes. The expression of RAGE was also markedly raised in active white matter lesions and localized to macrophages and activated microglia, which was also confirmed by the use of double immunofluorescence labeling. Demyelinated lesion center devoid of immune cells and activated microglia and macrophages rim are used to characterize the analysis of chronic activated MS lesions [87]. The expression of S100B was raised throughout the demyelinated areas. S100B is elevated in CSF, serum and post-mortem plaques of MS patients being related to demyelination and glial reactivity. Barros *et al.* showed that neutralization of S100B has a beneficial effect in an *ex vivo* demyelinating model by targeting S100B with pentamidine that could prevent MS-related pathogenesis in the *ex vivo* model. Pentamidine not only prevents demyelination and ax-

onal impairment but it also exacerbates the production of inflammatory factors (TNF-α, IL-1β, HMGB1). Also in the *in vivo* animal model of MS, the Experimental Autoimmune Encephalomyelitis, it was evaluated if pentamidine could prevent MS disease course [88]. EAE-induced animals given pentamidine reached a lower disease clinical score and provided fast recovery. Results show that S100B is involved in MS pathology and its inhibition may be a new possible therapy to decrease damage and improve disease recovery [79].

7. S100B IN TRAUMATIC BRAIN INJURY

TBI is a type of acquired brain injury from the external mechanical force that probably leads to permanent or temporary cognitive, physical and psychological functions impairment with or without loss of consciousness [89]. Pathologically, as found in brain injuries after acute ischemia followed by reperfusion, a decrease in the availability of oxygen disturbs the brain's energy balance and raises the ROS levels. Highly reactive chemicals such as ROS (NO, superoxide anion, and hydroxyl radicals) attack and damage DNA [90]. It has been reported that NO levels were raised with TBI demonstrating modulation of increased NO homeostasis. There is increasing evidence from experimental and clinical data that an inappropriate inflammatory response plays a major role in the pathology of TBI. Changes in levels of NO have also been linked with different forms of trauma including secondary damage after TBI [88]. Various studies have shown the upregulation of NO synthase enzymes, contributing to rises in the levels of NO in the brain, which leads to TBI-associated glutamate cytotoxicity including mitochondrial dysfunction pathogenesis. TBI is associated with elevated rates of NO in isolated organs, suggesting that TBI can cause systemic changes in NO regulation that can be beneficial or harmful [91].

Extracellularly administered S100B within normal and TBI state stimulates neurogenesis and neuronal plasticity as well as improves neuro-modulating functions involved in learning and memory [52]. S100B performs a dual function that at low concentration,t is beneficial and at higher concentration, the effects are harmful [92, 93]. Rapidly increasing extracellular levels of S100B have shown to result in cell death and neuronal dysfunction because of an inflammatory response that activates astrocytes, microglia along with extracellular elevation in calcium level and nitric oxide level [94, 95]. The BBB of the patient suffering from TBI gets disrupted causing the leakage of proteins from CSF following cerebral deterioration and formation of edema [96]. The albumin ratio between CSF: serum (Q_A) is sometimes used to detect the degree of disruption of BBB [97]. Some authors claim that through the disrupted BBB, S100B is released into the serum. The concentration of S100B in the CSF could be up to 100 times higher than in serum [98].

8. S100B IN SCHIZOPHRENIA

Schizophrenia is a severe mental illness with a variety of symptoms that affect cognitive function, perceptual experi-

ences, speaking and other behavioral activities. Schizophrenia has become a severe public health problem and exerts enormous economic and personal burden worldwide [99]. Astrocyte and oligodendroglial cells mediated increased S100B release may lead to neuroinflammatory processes by the activation of microglial expression of COX-2 and iNOS causing dysfunction of neurons and apoptosis [100]. NO is an important NMDA receptor activating the second messenger, which interacts with pathways of dopamine and serotonin, and the abnormal activity associated with these pathways is suggested to be implicated in the schizophrenia pathophysiology [101]. NO also performs uptake, storage and release of neurotransmitters and mediators such as acetylcholine, GABA, glutamate, noradrenaline, glycine and taurine. Furthermore, NO gets diffused across the cell membranes to activate their own receptors extrasynaptically. Studies expose the significant disturbed levels of NO in the structures of the brain such as the hypothalamus, striatum hippocampus, cerebellum and fluids of schizophrenic patients. These changes may lead to neurodevelopment alterations related to schizophrenia [102]. S100B has been proposed as a marker of astrocyte activation and brain dysfunction. Preclinical studies and clinical reports of schizophrenia and concentration of S100B are very consistent. Schizophrenia patients have higher S100B concentrations than healthy controls [103]. Green *et al.* studied the increased concentration of S100B proteins in the CSF of schizophrenia patients that could be related to an increased permeability of BBB in disease state [104]. Similarly, increased expression of S100B has been detected in cortical astrocytes of paranoid schizophrenia cases, while decreased oligodendrocytic expression has been observed in residual schizophrenia. 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 [105]. S100B is highly expressed in astrocytes and to a lesser extent in certain neuronal populations as oligodendrocytes and adipocytes. Elevated serum level of S100B in schizophrenia is correlated with insulin resistance. In fact, increased glucose and C-peptide levels were observed in the schizophrenia cohort and C-peptide/ glucose ratios predicted S100B levels [105].

9. S100B IN EPILEPSY

Epilepsy is a neurological disorder characterized by recurrent and spontaneous seizures caused by excessive, abnormal, and hypersynchronous neuronal discharge [106]. An imbalance between the excitatory glutamatergic and inhibitory GABAergic neuronal discharges causes brain damage and cell loss [107]. Astrocytes, a subtype of glial cells, play an important role in regulating cerebral ion homeostasis, transmitter regulation, maintenance of the blood-brain barrier (BBB), and structural, as well as metabolic support of neuronal cells. Recent evidence has indicated that the blood-brain barrier (BBB) dysfunction contributes to an etiological fac-

tor of seizures [108]. Alteration of BBB permeability is associated with seizure activity. In addition, it was demonstrated that BBB permeability can be assessed by measuring the serum level of the protein S100B released by astrocytes [109].

Several studies have revealed that the increase in the level of S100B in the CSF and temporal lobe of the epileptic patients may be the result of the elevated production or release by the dysfunctional astrocytes. A higher level of S100B can also elevate NO expression and induce the death of astrocyte cells [110]. NO causes the loss of neurons and leads to reactive glial cell proliferation, thus potentially participating in the epilepsy pathogenesis. There are earlier studies that report the NO inhibition to prevent convulsions [111].

Epilepsy animal model and post-surgery brain specimens from epilepsy patients have also indicated increased levels of S100B in brain tissue [112]. Available reports on S100B demonstrated different S100B levels in epilepsy. Portela *et al.*, in 2003, reported the normal level of serum S100B protein in focal epilepsy patients and Lu *et al.*, in 2010, reported increased levels of plasma S-100B in patients with MTLE as compared with the normal patient [113, 114]. Tergau *et al.* reported high levels of CSF S100B in temporal lobe epilepsy patients compared to controls [108]. In the study by Lu *et al.*, the S-100B protein concentration was shown to correspond with the epilepsy severity and hippocampal sclerosis patients had higher levels of plasma S100B than those with MTLE without hippocampal sclerosis [115]. An increased serum concentration of S100B may be a characteristic of neuronal damage in an epileptic brain [116]. Increased S100B serum levels have been observed in children with temporal lobe epilepsy. Atici *et al.* reported that levels of S100B protein were normal following a seizure in patients with simple febrile convulsions [117]. Furthermore, recently, Calik *et al.* demonstrated similar results from a study examining the serum and CSF levels of S100-B protein in children with febrile convulsions [118]. Griffin *et al.* reported high levels of S100B proteins in patients with epilepsy and S100B protein could be a significant factor in the epilepsy pathophysiology [119].

CONCLUSION AND FUTURE PERSPECTIVES

The S100B is a RAGE and TLR-4 receptor-binding protein that initiates multiple intracellular signaling pathways and regulates transcription factors leading to MAPK pathway activation resulting in cell survival, proliferation and gene up-regulation. The Zn^{2+} and Ca^{2+} binding S100B protein producing NO in response to iNOS can lead to excitotoxicity, inflammation, oxidative stress and mitochondrial dysfunction that leads to neuronal death in PD. Extracellularly administered S100B has shown to produce a beneficial effect in TBI stimulating neurogenesis, neuronal plasticity with learning and memory improvement. An increased serum concentration of S100B has been reported as a characteristic of neuronal damage in MS and epileptic brain.

The useful biomarker S100B in the pathology of a neurological disorder can be used as a diagnostic parameter as
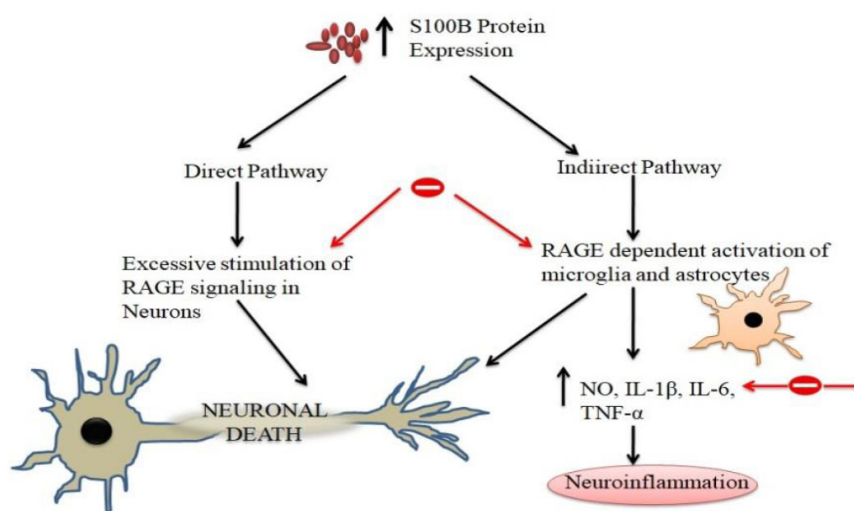
Fig. (4). Drug targets for S100B protein to prevent neuroinflammation and neurodegeneration. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

well as therapeutic targets in neuroscience studies. S100B has shown dual actions at low and high concentrations, being neurotrophic and neurotoxic respectively. Serum S100B level is a useful marker found in the pathology of various neurological disorders. An elevated level of protein initiates an inflammatory cascade that worsens the disease condition. So, targeting S100B and its receptor RAGE could be beneficial for the treatment of neurological disorders (Fig. **4**).

LIST OF ABBREVIATIONS

CNS	=	Central Nervous System
MAPK	=	Mitogen Activated Protein Kinase
NF-kB	=	Nuclear Factor Kappa Beta
CSF	=	Cerebrospinal Fluid
TNF	=	Tumor Necrosis Factor
AD	=	Alzheimer Disease
PD	=	Parkinson Disease
TBI	=	Traumatic Brain Injury
GPAF	=	Glial Fibrillary Acidic Protein.
GAP-43	=	Growth Associated Protein:43
5-HT	=	5-Hydroxy Tryptamine
IL-1	=	Interleukin 1
MPTP	=	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
iNOS	=	Inducible Nitric Oxide Synthase
RAGE	=	Receptor for Advanced Glycation End Product
IL-6	=	Interleukin 6, IL-1B: Interleukin 1 Beta
M-CSF	=	Macrophage Colony-Stimulating Factor

AGEs	=	Advanced Glycation End Products
TTR	=	Transthyretin
HMGB1	=	High Mobility Group Protein B1
ROS	=	Reactive Oxygen Species
NFT	=	Neurofibrillary Tangles
NK cells	=	Natural Killer cells
CD8+	=	Cluster of Differentiation
TLR-4	=	Toll Like Receptor-4
mRNA	=	Messenger Ribonucleic Acid
APP	=	Amyloid Precursor Protein
MS	=	Multiple Sclerosis
PLP	=	Proteolipid Protein
BBB	=	Blood Brain Barrier
MTLE	=	Mesial Temporal Lobe Epilepsy.

AUTHORS' CONTRIBUTIONS

Singh. S worked on conception, designing, framing of the review, and supervised, analyzed and finalized the manuscript and Urvashi wrote the paper.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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