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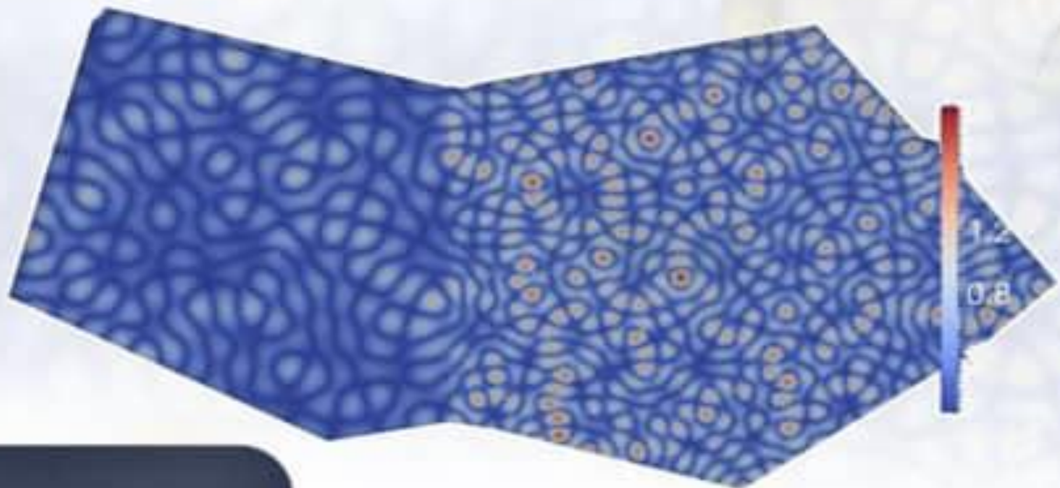

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The Fundamental Role of Neuroinflammation at the Beginning and Progression of Alzheimer's Disease

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The majority of astrocytes are responsible for the expression and release of S100B, a 21-kDa calcium-binding protein of the EFhand type (helix E-loop-helix F). It is mostly present in the neurological system and, depending on concentration, has different (beneficial, detrimental) effects on neurons, astrocytes, and microglia. an effect on the survival and development of both glia and neuronal cells. Patients with Down Syndrome and Alzheimer's Disease (AD) have brains that are overexpressed with the S100 protein Down Syndrome (DS). Increased S100B concentrations are linked to brain trauma and ischemia, most likely due to astrocyte destruction. As S100B appears to influence multiple neuropathological mechanisms in (AD) , a pivotal role for S100B as a significant contributor to (AD) pathology has emerged.
Studies of S100B overexpression, S100B localization, multiple relationships between S100B and increase amyloid precursor protein, the interaction between S100B and dystrophic neuritis plaques, and change in a neurofibrillary tangle in Alzheimer's disease focus on providing evidence for the involvement of S100B in Alzheimer's disease pathology and neuronal loss. The significance of S100B in head trauma and degenerative brain disease is the central subject of this review. Overexpressing s100B, which also causes more astrogliosis and microgliosis, speeds up the pathogenesis of Alzheimer's disease. Numerous clinical problems have been associated with an increase in S100B, a neurotropic signaling protein.

1 Introduction

The AD is a chronic, progressive loss of basal forebrain cholinergic neurons, and irreversible neurodegenerative disease with clinical characteristics of memory loss, dementia and impairment in memory, visuospatial skills, complex cognition, language, emotion and personality. Prominent neuropathologic features of AD are senile plaques, neurofibrillary lesions, synaptic and neuronal loss, and gliosis, destroys the higher structures of the brain. The formation of amyloid plaques and neurofibrillary lesions are thought to contribute to the neurodegeneration in the brain of Alzheimer's disease sufferers play an important role in the inflammatory response in the central nervous system (CNS) and in AD pathogenesis. cognitive dysfunction concomitant with the accumulation of senile plaques (SP) is consist of Beta-amyloid (Aβ) plaques (extracellular Aβ deposition) and neurofibrillary tangles (NFT, intracellular deposits of hyper-phosphorylated tau

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protein) have been identified as two classical pathological hallmarks of AD. Accordingly, numerous studies have focused on Aβ generation and deposition as well as on NFT formation as the triggering factors for AD occurrence. Gliosis is also seen in AD: activated astrocytes and microglia are characteristically found in abundance near neurons and plaques, and this can be seen even in a case described by Alzheimer in1911.This suggests that inflammation maybe involved in AD, because glial cells mediate the innate immune response in the central nervous system. When activated, astrocytes and microglia produce several proinflammatory signal molecules, including cytokines, growth factors, complement molecules, and adhesion molecules. Of particular interest in AD are the cytokines S100B, which is mainly produced by astrocytes, and interleukin1(IL-1), which is mainly produced by activated microglia.

Role of Astrocytes in Alzheimer's Disease:

Histo-pathological features of AD include large extracellular senile plaques (SPs) composed of the amyloid-β (Aβ) plagues and neurofibrillary tangles, which (Wyss-Coray and Rogers, 2012) are intra cellular inclusions of hyperphosphorylated tau protein in selective regions of the brain (Xiao *et al*, 2014) (Wyss-Coray and Rogers, 2012) β -amyloid is a peptide of 42 amino acid residues produced by the selective photolytic cleavage of transme brane amyloid precursor proteins (APP) by β and γ-secretases. Aβ can directly induce (Sidoryk-Wegrzynowicz *et al* 2011) neuronal cytotoxicity, but the relevance of such toxicity to the disease is controversial[1]. Morphological characterization of GFAP-positive astroglial cells performed on AD mouse model at different ages showed an age-dependent reduction in GFAP expression. These authors suggested that in an AD transgenic, reactive hypertrophic astrocytes surround the neuritic plaques whereas astroglial cells in other brain regions undergo atrophy, which may account for early changes in synaptic plasticity and cognitive impairments inherent to AD. In the AD human tissue ,prominent astrogliosis occurs in the cells surrounding amyloid plaques, and these activated astrocytes accumulate large amounts of Ab42, which are derived from neuronal debris and associated with plaques (Andrea *et al*, 2004) . Moreover, astrocytes from patients with dementia show significantly decreased complexity compared to the healthy brain (Sidoryk-Wegrzynowicz *et al* 2011). It is widely recognized that age is the most important risk factor for AD and that the innate immune system plays a role in the development of neurodegeneration. Very little information is available on how aging affects the innate immune system. However, there are clear indications that the development of AD is due to age-related changes that modulate innate immunity. It is interesting that Aβ and other proteins found in the senile plaques of AD patients are potent activators of the innate immune response because chronic stimulation of the innate immune system may lead to alterations of astrocytes. When the brain is injured, astrocytes are believed to react by putting down glial scar tissue as part of the healing process. Recently, it has been shown that astrocytes themselves actively contribute to the inflammatory response (Sidoryk-Wegrzynowicz and Aschner 2014). It has been shown that the neurotransmitter glutamate is released in neuroinflammatory conditions and to some degree under normal circumstances, which on the long term is proved to be toxic to neurons. The neuroprotective action of astrocytes has also been attributed to their capacity to take up the neurotransmitter glutamate, convert it to glutamine, and recycle it to neurons (Vesce *et al*, 2007).

Neuroinflammation and immune system crosstalk in Alzheimer disease:

Neuroinflammation is the mechanism of CNS inflammation that occurs in response to trauma, infections, and/ or neurodegenerative diseases. In neuroinflammation, cellular and molecular immune components such as specialised macrophages (microglia), cytokines,chemokines complement, tumor necrosis factor (TNF) (Allen *et al*, 1999) recruited from the peripheral system following disruption of the blood-brain barrier. Alterations in the permeability of the BBB and chemotaxis may permit the recruitment and passage of peripheral cells into the brain parenchyma. Determining the detailed mechanism of this process is an active area of research. Investigators are exploring the processes involved in both the passage of inflammation into, and the effect of cytokines on, the central nervous system (CNS) (Fung, *et al* 2012). This in turn leads to the activation of the glial cells, such as microglia and astrocytes. The effect of neuroinflammation is considered neuroprotective when the inflammatory activity is for a shorter period of time whereas chronic neuroinflammation is associated with harmful consequences for the CNS. (Allen *et al*, 1999) (Boulanger *et al*, 2001). In the brain, inflammation is mediated largely by glial cells, the support cells of the nervous system. Glial cells include astrocytes, which support neuronal metabolism, oligodendrocytes which produce myelin insulation for nerve cells (allowing more efficient conduction of nerve impulses), and microglia, which serve as a kind of immune system. Glial cell activation is a key feature of brain inflammation. When activated, microglia produce inflammatory mediators that activate more cells to produce additional inflammatory mediators. These mediators can thus create positive feedback loops, thereby amplifying inflammation. Brain inflammation, including increased microglia and astrocyte (Joseph *et al*, 2005) activation, generally increases as part of the aging process and brain inflammation is a key feature of neurodegenerative diseases, including AD. The immune system comprises a complex interrelated network of cellular, molecular, and chemical mediators that function to protect the body against environmental stress factors. These stressors can be as diverse as microorganisms (viral, bacterial, fungal agents), physical damage (burns, lacerations), or environmental toxins (snake venoms, nonessential metals, chemicals). To combat all these stressors, the first line of defense is innate or natural immunity. The inflammatory component of this response is important in recruiting cells of the immune system to the compromised area, and cytokines and chemokines mediate this function. Cytokines orchestrate a specific response that is appropriate based on the type of foreign antigen that has penetrated the tissue, and chemokines are important in allowing cells of the immune system to reach the area under attack (Campbell, 2004), some endogenous factor are response by inhibition proinflammatory gene expression via negative feedback inhibition (Nadeau and Rivest, 2003) however, over activation of innate immunity can lead to neurodegenerative disorders which is accompaniedby enhanced expression level of S100B and S100B receptor ,RAGE in neural and inflammatory and cytokines and chemokines e.g TNF ,IL-1,S100B. have been implicated as etiological factors in a variety of neurological disease states including AD (Huell *et al*, 1995).

Relationship between S100, Interleukin 1, and Alzheimer Disease:

S100B in Alzheimer Disease:

S-100B proteins, named for their solubility in a 100% saturated solution of ammonium sulphate at neutral pH (Sindic *et al*, 1982). It is belong to a group of closely related, small, acidic, water-soluble, Ca^{2+} -binding proteins (Mata *et al*, 1990) (Zimmer *et al*, 1995). A great body of evidence suggests that S-100 could be viewed as a multifunctional subfamily of Ca2+-binding proteins of the EF-hand type. A large number of diverse functions is attributed to S-100 proteins, ranging from calcium-buffering through intracellular (e.g., modulation of enzyme activities, energy metabolism, motility, and secretion cell proliferation and differentiation, cytoskeletal assembly and disassembly) and nuclear (e.g., transcription and apoptosis) functions to extracellular activities (e.g., secretion, neurite extension, calcium homeostasis and chemotaxis) (Donato 1999). S100B, one of the originally described S100 proteins, is abundantly expressed by central and peripheral nervous system glia, and to a much lesser extent, by some populations of neurons (Ichikawa *et al*, 1997) (Yang *et al*, 1995) S100B is detected in varying abundance in a limited number of brain cells including astrocytes, maturing oligodendrocytes, neuronal progenitor cells, pituicytes, ependymocytes, and certain neural populations. Although the majority of astrocytic S100B localizes within the cytoplasm, 5%–7% is membrane bound. S100B is also expressed by non-neural cells, including melanocytes, chondrocytes, and adipocyte (Donato 1999). increased S100B levels are also found in the cerebral spinal fluid of A.D patients (Peskind *et al*, 2001) Astrocytic S100B is considered to be the major factor contributing to the formation of dystrophic neurites, which are pathologically transformed neurites concentrated around amyloid plaques (Mrak *et al*, 2005) (Cairns *et al*, 1992) AD neuropathological hallmarks include brain deposition of amyloid-β (Aβ) peptide as senile plaques, accumulation of abnormal tau protein filaments as intracellular neurofibrillary tangles, extensive neuronal degeneration and loss, profound synaptic loss, and β-amyloid plaque associated astrocytosis and microgliosis (Zhang and Song 2013) (Selkoe, 2001) S100B release is driven by the developmental stage of the astrocytes (Van Eldik and Zimmer, 1987) and metabolic stress (oxygen, serum, or glucose deprivation) (Gerlach *et al*, 2006) S100B can also be released in response to external stimuli such as glutamate (Ciccarelli *et al*, 1999) serotonin (Whitaker-Azmitia *et al*, 1990) ,the pro-inflammatory cytokines TNF-alpha (Edwards and Robinson, 2006) and IL-1beta (de-Souza *et al*, 2009), beta-amyloid peptides (Peña *et al*, 1995) ,1-methyl- 4-phenyl 1,2,3, and 6 tetrahydropyridine (MPTP) (Iuvone *et al*, 2007), forskolin, lysophosphatidic acid (Pinto *et* *al*, 2000) .Local synaptic responses with local overexpression of the Aβ precursor protein and local astrocyte activation with over expression of S100B might then be responsible in part for the progression of pathology across brain regions in Alzheimer's disease.

Interleukin-1:

Interleukin-1 was first described in 1972 as a lymphocyte activating factor (Gery and Waksman 1972) and later was shown to exert a variety of effects including induction of inflammation, body temperature increase, proliferation of T and B cells, induction of acute phase proteins and prostaglandins and regulation of hematopoesis. Its activities are not restricted to the immune system. Interleukin-1 is also involved in the regulation of blood calcium levels, stimulation of proliferation of various cells, regulation of blood pressure or modulation of sleep. However, IL-1 represents one of the most important mediators of the inflammatory response that induces a cascade of proinflammatory effector molecules (Sharma 2011). Interleukin-1 (IL-1) has been implicated in a number of neurodegenerative conditions and is generally believed to have neurotoxic actions, although the mechanisms of these effects are unclear (Zilka 2006). There are two molecular forms (ILla and IL- IB), that is secreted by microglia and astrocytes. IL- 1 produced by activated microglia may trigger production of other cytokines, such as IL-6, TNF-a by astrocytes and other cells.

Furthermore, IL-1 induces astrocytes and neurons to produce more B-amyloid which leads to deposition of amyloid fibrils (Zilka 2006). Through various pathways, IL- 1 causes neuronal death, which activates more micrglia, which in tum releases more IL-1 in a self-sustaining and self-amplifying fashion. Interleukin-6 (IL-6) is a multifunctional cytokine that stimulates the acute-phase reaction, which enhances the innate immune system and protects against tissue damage. IL-6 is synthetised by microglia, astrocytes, neuronal and endothelial cells. In certain condition, IL-6 may have inflammatory or immunosuppressive effects (Klegeris and McGeer 2005) IL-6 seems to act as a secondary process amplifying the inflammatory response initiatedby IL- IB (Lee *et al*, 1993). Elevated levels of IL-6 mRNA were demonstrated in the entorhinal cortex and the superior temporal gyrus of AD patients (Y.-W. GE and LAHIRI 2002) IL-1 is markedly overexpressed by activated microglia in Alzheimer's disease (Shaftel *et al*, 2008) and, like activated astrocytes, these activated microglia show characteristic patterns of association with different stages of A neuritic plaques. and enhances production and processing of (β-amyloid precursor protein (β-APP). A major inducer of astrocyte activation and S100B expression is the immunomodulatory cytokine IL-1 (Giulian *et al*, 1988) (Sheng *et al*, 1996). Activated Microglia overexpressing IL-1, like activated astrocytes overexpressing S100B, are frequently found in the early nonfibrillar amyloid deposits of Alzheimer's disease (Griffin *et al*, 1995) (Mackenzie et al, 1995). These proposed pathogenic mechanisms elevated levels of the inflammatory cytokine IL-1 drive S100β and β-APP overexpression and dystrophic neurite formation in Alzheimer's disease. interact with other cellular and molecular factors to form a cytokine cycle of molecular cascades with feedback amplification of glial activation and with progressive neuronal injury (Griffin and Mrak 2002) (Mrak and Griffin 2000). In moreover to the previously mentioned, S100B-mediated effects on free calcium levels and on dystrophic neurite formation within neuritic A plaques, there are other consequences of cytokine cycle activation. IL-1 expression (Mrak 2001). Astrocytic S100β, in turn, i) increases intracellular free calcium concentrations, ii) promotes growth of neuronal processes that, coincidentally, necessitate further neuronal expression ofβ-APR favoring release of neurotoxic β-amyloid; and iii) induces astrocytic nitric oxide synthase activity with release of potentially neurotoxic nitric oxide. The resultant neuronal cell dysfunction and death, together with β-amyloid activation of the classical complement pathway microglial IL-1 overexpression i) promotes astrocyte activation and upregulates astrocytic expression of S100β, ApoE, α1-antichymotrypsin and the complement protein C3; ii) stimulates neuronal synthesis and processing ofβ-APP; and iii) has autocrine effects to activate microglia and to further promote IL-1 expression (Hu and Van Eldik 1999).

Rage in Alzheimer disease:

Non-enzymatic glycosylation theory of aging' proposed that the AGE-mediated crosslinking of long-lived proteins contributes to the age-related decline in the function of cells and tissues in normal aging (Monnier and Cerami, 1981), AGEs and S100B are also abundant in the nervous system, therefore their interaction with RAGE appears to be implicated not only to the pathology of amyloid-type disorders, but with other neurodegenerative disorders such as Huntington's disease (HD) Parkinson's disease (PD) and amyotrophiclateral sclerosis (ALS) (Ma and Nicholson 2004). RAGE expression, apart from neurons, microglial cells astrocytes in the healthy human brain (Brett *et al*, 1993). The involvement of AGEs in brain aging and – in an accelerated fashion – in AD was first proposed in the mid-1990s (Takeda *et al*, 2014) The stability of proteins that constitute the long-lived intracellular (neurofibrillary tangles and Hirano Bodies) and extracellularn protein deposits (senile plaques) suggests that they would be ideal substrates for glycation, a process that occurs over a long time, even at normal levels of glucose, ultimately resulting in the formation of AGEs. establishing a link between the expression of RAGE and the pathophysiological changes in AD, showed that extracellular deposition of Aβ and its interaction with the brain vasculature or directly with neurons and microglia, lead to neuronaldysfunction. The latter dysfunction was mediated by RAGE in a dose dependent manner and moreover, binding of Aβ to RAGE generated oxidative stress, activation of NF-kB and induced expression of macrophage-colony stimulating factor (M-CSF) (Onyango *et al*, 2005). AGE harmless post-translational protein modification; various pathophysiological effects have been found at the cellular and molecular level. One of the proposed mechanisms of AGE-induced damage are reactive oxygen species (ROS), particularly superoxide and hydrogen peroxide released by AGEs (Guglielmotto *et al*, 2010). The activation of microglial RAGE by many of its ligands, including AGEs andAβ, results in the release of proinflammatory mediators such as free radicals and cytokines (Guglielmotto *et al*, 2005). Additionally, in astrocytes of AD brain, epitopes of Aβ, AGEs and RAGE were found to co-localize, suggesting a potential participation in the pathogenesis of the disease (Sasaki *et al*, 2001), microglia had increased expression levels of IL-1 and TNF-α, suggesting an inverse correlation between cytokine production and Aβ clearance. These data indicate that, although early microglial recruitment promotes Aβclearance and is neuroprotective in AD, as the disease progresses, proinflammatory cytokines are produced in response to Aβdeposition (with RAGE as the A β-binding receptor), which then downregulate genes involved in A β clearance and promote Aβ accumulation. Microglia may thus contribute to plaque formation, accumulation of AGEs on plaques over time, more intense crosslinking, inflammation and chronic neurodegeneration. As S100 proteins and especially S100B are abundantly expressed in the nervous system, Huttunen and his coworkers initially suggested that RAGE, already known to interact with Aβ, can also mediate neurotoxicity due to elevated levels of S100B, shedding new light on studies of the molecular pathophysiology of AD (Sindic *et al*, 1982). S100B stimulated NF-kB transcriptional activity in microglia in a manner that was strictly dependent on RAGE, therefore pointing to additional RAGE-mediated effects on microglia activation withimpact in AD and other neurodegenerative disorders (Adami *et al*, 2004).

Conclusion and perspective:

In order for the human nervous system to operate normally, astrocytes are essential. They also play a crucial role in neurodegenerative illnesses and coordinate many of the first and ongoing astrocyte responses to injury. Certain neurological illnesses primarily involve astroglial cells, Astrocytes control synaptic transmission and plasticity, safeguard neurons from harmful substances, and provide metabolic support for neurons to guarantee their proper operation. By providing growth factors and cytokines chemokines and IL-1α astrocytes are involved in all types of neurodegenerative processes, and display prominent remodelling in the AD; early dystrophic changes in astroglia can represent an important step in initiation and progression of Alzheimer's disease. Targeting of astroglia may provide a new principle for treatment of AD at the early stages of the disease.

Conflict of interest: The authors declare that there are no conflicts of interest.

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