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## RAGE is a key cellular target for A $\beta$ -induced perturbation in Alzheimer's disease

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### Abstract

RAGE, a receptor for advanced glycation endproducts, is an immunoglobulin-like cell surface receptor that is often described as a pattern recognition receptor due to the structural heterogeneity of its ligand. RAGE is an important cellular cofactor for amyloid  $\beta$ -peptide (A $\beta$ )-mediated cellular perturbation relevant to the pathogenesis of Alzheimer's disease (AD). The interaction of RAGE with A $\beta$  in neurons, microglia, and vascular cells accelerates and amplifies deleterious effects on neuronal and synaptic function. RAGE-dependent signaling contributes to A $\beta$ -mediated amyloid pathology and cognitive dysfunction observed in the AD mouse model. Blockade of RAGE significantly attenuates neuronal and synaptic injury. In this review, we summarize the role of RAGE in the pathogenesis of AD, specifically in A $\beta$ -induced cellular perturbation.

### Keywords

Amyloid beta; RAGE; Alzheimer Disease; Inflammation; Review

## 2. Introduction

Alzheimer's disease (AD) is the most common form of dementia affecting the elderly. Clinically, AD is characterized by a progressive decline in cognitive function characterized by memory loss as well as personality changes. AD is pathologically characterized by the presence of senile plaques containing amyloid- $\beta$  (A $\beta$ ) protein and neurofibrillary tangles that consist mainly of intracellular and abnormally phosphorylated tau protein (1-6), as well as severe gliosis in the cerebral cortex and the hippocampus (7). Recent studies suggest an increase in inflammatory responses such as an increase in production of proinflammatory mediators, microglial infiltration and activation, and levels of several S100 calcium-binding proteins (S100B, S100A6, S100A9, and S100A12) in the AD brain.

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A $\beta$  is a neurotoxic peptide, the accumulation of which leads to cellular perturbations including impaired energy metabolism and mitochondrial respiratory function, increased oxidative stress, neuroinflammation, synaptic failure, and neurodegeneration (6, 8-15). Proteolytic cleavage of the transmembrane  $\beta$ -amyloid precursor protein (APP) leads to generation of 1-40 or 1-42 amino acid A $\beta$ , which can form soluble oligomers, beta sheets containing fibrils, and insoluble aggregates (7). Accumulation of A $\beta$  in the brain plays a key role in the development of AD and the mutation in APP increases A $\beta$  accumulation in the brains of AD patients and transgenic AD mice (9, 16). In fact, multiple lines of evidence frame A $\beta$  oligomers and A $\beta$  fibrils as the main culprits behind the synaptic dysfunction and neuronal death observed in AD patients (7). Oligomer A $\beta$  interferes with long term potentiation (LTP) and cognitive processes, suggesting the causal role of A $\beta$  peptides in the neuronal dysfunction that characterizes the early stages of AD (17-21). However, the mechanisms underlying A $\beta$ -mediated neuronal and synaptic dysfunction have not yet been fully elucidated.

As expected for a pleiotropic peptide such as A $\beta$ , many cell surface interaction sites and intracellular proteins have been reported, ranging from cell surface receptors, such as receptor for advanced glycation endproducts (RAGE) (10, 17-22),  $\alpha$ -7-acetylcholine receptor ( $\alpha$ 7-nAChRs) (23), type A macrophage scavenger receptor (MSR) (24), integrins (25), insulin receptor (26), and P75 neurotrophin receptor (P75NTR) (27-28), LRP-1 (29) to cell-associated proteoglycans (30), mitochondrial proteins, such as amyloid- $\beta$  (A $\beta$ ) peptide-binding alcohol dehydrogenase (ABAD) (31-35) and cyclophilin D (5, 9). The pathogenic significance of these interactions remains to be further defined. It is likely that several cell cofactors contribute to the various cellular effects of AB. Thus, to gain further insight into this complex system, these interactions must be dissected at the level of the individual cellular cofactor.

### 2.1. Structure of RAGE

RAGE has several isoforms, each with a distinct tissue-specific expression pattern (7). Among the various alternatively spliced isoforms of RAGE, two prevalent isoforms are full-length RAGE and the secreted isoform of soluble RAGE (7). Full-length RAGE is composed of an extracellular element consisting of one Ig-like V-domain followed by two Ig-like C-type domains, a transmembrane domain consisting of a single helix and a short cytosolic domain, which allows for signal transduction (7-8). Soluble RAGE (sRAGE) consists solely of the extracellular part including V, C1, and C2 domains with no transmembrane domain, and is thus released into the extracellular space (7). X-ray crystal structure analysis demonstrated that V and C1 domains comprise the S100B binding domain through a highly electropositive surface (36, 37). The same domain is presumed to also bind A $\beta$ , which is known to be negatively charged. Additionally, the structural data suggest that RAGE has features typical of I-set topology, which is characteristic for cell adhesion molecules and ligand-induced oligomerization within cytoplasmic membrane might be the mechanism for its activation (37).

## 3. The Role of RAGE in the A $\beta$ -Induced Cellular and Molecular Events Relevant to the Pathogenesis of Alzheimer's Disease

### 3.1. Increased expression of RAGE in Alzheimer's disease

Studies on human AD brains reveal increased RAGE expression in neuronal, microglial and endothelial cells when compared to age-matched control subjects without AD (7, 18, 38-39). Cells around senile plaques express higher levels of RAGE during disease progression (7). Increased RAGE expression was found in microglia from AD brains when compared to those from age-matched, nondemented control brains (18, 38). Lue and colleagues reported

that microglia in AD-affected regions, including the hippocampus, had higher levels of RAGE in the AD brains than that in the age-matched non-AD controls. Furthermore, expression levels of RAGE are correlated to the severity of the disease (clinical score of the amyloid plaque and tangle, respectively) (38). Similarly, vasculature with A $\beta$  deposits from an AD patient also displayed increased RAGE antigen as compared to age-matched non-AD controls (18, 38-41). In the recent study, Lue and colleagues reported a 60% increase in RAGE protein levels in the blood vessels from cerebral amyloid angiopathy (CAA) patients, compared with vessels from age-matched non-AD controls (42).

Meanwhile, expression of RAGE\_v1, the prevalent isoform of RAGE in endothelial cells and in the human brain, is reduced in hippocampal neurons of AD patients (43), since RAGE\_v1 is the dominant negative (ND) form of RAGE. Reduction of RAGE\_v1 may lead to sustained RAGE activation. On the other hand, the soluble isoform of RAGE (sRAGE) can prevent the adverse effects of RAGE signaling by acting as a decoy that binds to RAGE ligands thereby preventing the interaction of RAGE with its ligands. Recent studies comparing the concentration of sRAGE in the serum of patients versus controls in various pathophysiological condition, demonstrate both positive and negative correlation between the concentration of sRAGE and the severity of the disease (7). sRAGE levels were significantly reduced in the plasma of patients with AD or mild cognitive impairment (MCI) (44-45). Levels of sRAGE in the plasma are related to the level of cognitive impairment in AD and MCI patients (46). These results suggest that change in RAGE expression levels might impact the cellular perturbation relevant to the development and progression of AD. Recent studies suggest that the RAGE G82S polymorphism is associated with the AD. The plasma sRAGE levels were also lower in AD than in normal elderly controls and the presence of the risk allele was associated with further plasma sRAGE reduction and quicker/faster cognitive deterioration (47). Thus, the RAGE G82S variant might be involved in genetic susceptibility to AD.

In a transgenic AD mouse model, RAGE expression was elevated in mice expressing a mutant form of human APP (mAPP). Increased levels of RAGE were observed in the neurons and microglia of these animals as they age and accumulate A $\beta$  (8, 19, 38).

### 3.2. RAGE-A $\beta$ interaction mediates neuroinflammation

Deficient as well as excessive responses in neuroinflammation and microglial activation can result in pathological conditions (8, 48-50). The innate responses of glia to injury, foreign pathogen, or activating stimuli generally lead to beneficial outcomes, such as phagocytosis or production of reparative or protective factors; however, sustained activation of microglia and overproduction of proinflammatory mediators disturbs homeostasis, resulting in disease progression and exacerbation of induction factors that influence the severity of neuronal dysfunction and the progression of neuropathology (8, 48, 51-55). The precise mechanisms by which A $\beta$  mediates activation of microglia and astrocytes remain to be elucidated. It appears that there is an important role for RAGE-mediated signaling in the microglial activation and neuronal dysfunction relevant to AD pathology.

Microglia play a critical role in A $\beta$ -mediated neuronal perturbation and death present in the pathogenesis of AD. Many inflammatory mediators detected in AD brains are of microglial origin (8, 50, 55-59). Increased microglial activation, microglial association with senile plaques, and elevated levels of proinflammatory mediators (i.e. cytokines, chemokines and free radicals) have all been observed in the AD brain and AD mouse models and evidence indicates that the aforementioned contribute to neuronal damage (8, 49, 61). Pathological analyses of brains from AD patients and AD-type-mouse models (including transgenic mouse systems and direct infusion of A $\beta$  into brain parenchyma) show that activated microglia and astrocytes accumulate to the greatest extent in the proximity of amyloid

plaques (8). Studies carried out with an *in vitro* cell culture model show that direct administration of A $\beta$  to multiple cell types can induce cellular stress, and this effect is probably increased in the presence of activated microglia (8, 38).

RAGE triggers the generation of proinflammatory cytokines at the blood brain barrier (7). Lue and colleagues cultured microglia from AD and control brains to show that increases in macrophage-colony stimulating factor (M-CSF) production in the presence of A $\beta$ 1-42 in AD-derived microglia was a RAGE-dependent process (40). Further, in gene array studies of microglia retrieved from AD brains, there was an up-regulation of multiple proinflammatory cytokines and matrix metalloproteinases (40).

In the transgenic mouse model of AD, RAGE dependent signaling in microglia stimulates inflammatory responses and processes that exacerbate neuronal damage, ultimately impairing neuronal function (8, 38). Fang and colleagues demonstrated that overexpression of microglia RAGE in Tg APP mice exacerbates neuroinflammation, as evidenced by increased proinflammatory mediator production, A $\beta$  accumulation, impaired learning and memory, and neurotoxicity (8). Transgenic mice expressing human mutant APP in neurons and RAGE in microglia (mAPP/RAGE mice) display: 1) age-dependent enhancement of interleukin -1  $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor-  $\alpha$  (TNF- $\alpha$ ) production in the cerebral cortex, two months prior to that observed in mAPP mice; 2) increased plaque-associated microglial clusters and astrocyte infiltration when compared to mAPP mice at 9-10 months of age; 3) A $\beta$  accumulation; 4) reduced acetylcholine esterase activity; 5) and accelerated deterioration of spatial learning/memory.

Neuropathological changes are accelerated in mAPP/RAGE mice and occur as early as 4-5 months of age, whereas transgenic mutant APP mice do not display such abnormalities at that age. Introduction of the DN-RAGE transgene, a signal transduction-defective mutant form of RAGE, into the microglia of mAPP mice delayed and attenuated increases in brain cytokine levels as well as the deterioration induced by A $\beta$  from 2 to 10 months of age. Notably, in the absence of RAGE ligands, it does not appear that DN-RAGE or RAGE has an effect on cytokine production, as evidenced by the comparable levels of IL-1 $\beta$  and TNF- $\alpha$  among single Tg RAGE, DN-RAGE and nonTg littermate controls (8). mAPP/DN-RAGE mice do not show significant microglial and astrocyte infiltration in the cerebral cortex and hippocampus. Introduction of DN-RAGE into mAPP mice may exert a protective effect against accelerated learning and memory deterioration.

Extensive evidence supports the theory that the p38 MAPK (mitogen-activated protein kinase) signaling cascade contributes to cytokine overproduction and the neurodegenerative effects seen in AD (8, 20, 54-55, 62-63). For instance, activation of p38 MAPK was found in early stage AD brain and in an AD mouse model, while inhibition of p38 MAPK activation blocks A $\beta$ -mediated cytokine production and neuronal death (8, 19-20, 51-52, 64-65). In brains of mAPP mice with increased expression of microglial RAGE, levels of p38 and extracellular-signal-regulated kinases 1/2 (ERK1/2) phosphorylation were significantly higher when compared to the levels found in the brains of transgenic mAPP mice without over-expression of RAGE; cytokine production and exaggerated neuronal stress are also seen with increased microglial RAGE expression (8).

Since expression of microglial DN-RAGE in mAPP mice attenuates A $\beta$ -mediated detrimental effects, it has been suggested that RAGE-dependent activation of p38 and ERK1/2 MAPK pathways is at least partially responsible for A $\beta$ -mediated microglial activation and the induction of proinflammatory mediators (8). Fang and colleagues showed that phosphorylated p38 and ERK1/2 levels were significantly increased in brain extracts of mAPP and mAPP/RAGE mice, as compared to nonTg mice; further, mAPP/RAGE brains

exhibited even higher levels of phosphorylated p38 and ERK1/2 than the mAPP brain. mAPP/DN-RAGE mice showed significantly less p38 and ERK1/2 phosphorylation, as compared to mAPP/RAGE mice. Taken together, these findings indicate the existence of RAGE-dependent activation of MAPK p38 and ERK1/2 in microglia (8). Importantly, findings by Fang and colleagues also indicate that microglial RAGE contributes significantly to increases in neuroinflammation, A $\beta$  accumulation, and neuronal perturbation in an A $\beta$ -rich environment (8), suggesting that RAGE-dependent signal transduction in MAP kinase (i.e., p38 and ERK1/2) activation is an important mechanism underlying A $\beta$ -involved neuronal inflammation and neuronal injury.

Elevated levels of AGEs or A $\beta$  at sites of inflammation can trigger RAGE-dependent oxidative stress and NF- $\kappa$ B activation, which in turn leads to further increased RAGE expression because of the presence of NF- $\kappa$ B response elements within the promoter region of RAGE; thus, activation of RAGE sustains NF- $\kappa$ B activation (7, 19, 41). This process represents a potential positive feedback loop between RAGE, oxidative stress and inflammation. In various cell types, including neurons, endothelial cells and microglia, RAGE-A $\beta$  interaction can lead to the formation of reactive oxygen species (ROS), the activation of NF- $\kappa$ B, or the expression of cell adhesion molecules mediating the recruitment of inflammatory cells (7, 40-41). Interestingly, administration of sRAGE to cells *in vitro* or animals *in vivo* attenuates RAGE-mediated cellular perturbation. For example, transgenic APP mice that received sRAGE show significantly reduced amyloid accumulation in the brain and improved vascular and synaptic function (22, 66).

### 3.3. RAGE mediates neuronal and synaptic stress

The interaction of RAGE with A $\beta$  affects neuronal function as evidenced by *in vitro* cell culture (18, 41, 67-68) and *in vivo* animal model studies (17, 19-22). Studies on the AD-type mouse model provide substantial evidence that RAGE serves as a cellular cofactor in A $\beta$ -induced neuronal stress. Transgenic APP mice overexpressing neuronal RAGE and A $\beta$  (Tg RAGE/mAPP) exhibited earlier onset of spatial learning/memory function abnormalities and neuropathological changes as compared to animals expressing only mutant APP (19).

Analysis of synaptic function by measurement of synaptic transmission including both basal synaptic transmission (BST) and LTP states in the hippocampus including CA1 stratum radiatum, revealed that BST was abnormal in both transgenic mAPP mice and transgenic RAGE/mAPP mice, whereas LTP abnormality was observed in transgenic RAGE/mAPP but not in transgenic mAPP mice. These results imply that overexpression of neuronal RAGE in transgenic mAPP mouse brain accelerates synaptic dysfunction further impairing synaptic plasticity. In experiments to control for the effect of APP over-expression independent of A $\beta$  production, we tested learning memory performance with the radial-arm water-maze in transgenic RAGE/wild-type (wt) APP mice. These mice are known to produce much lower amounts of A $\beta$  1-40 and A $\beta$  1-42. We found that overexpression of wtAPP did not further impair learning and memory in transgenic RAGE/wtAPP mice. Thus, the effect of RAGE on spatial working memory is likely due to its interaction with the overproduction of A $\beta$ . Consistent with the results from behavioral and electrophysiological experiments, transgenic RAGE/mAPP mice displayed early changes in neuropathology and showed a decrease in acetylcholinesterase-positive neurites in AD-affected regions including subiculum, entorhinal cortex and CA1 region as early as 3-4 months of age, that then proceeded to develop cerebral A $\beta$  deposition. Notably, introduction of DN-RAGE into transgenic mAPP mice significantly improved learning/memory, preserved LTP, and alleviated neuropathology, suggesting the involvement of RAGE-dependent signal transduction in neuronal damage due to A $\beta$  (19).



Synaptic dysfunction is an early pathological feature of AD (69). Impaired memory and synaptic loss occur before extensive deposition of A $\beta$  in the brains of AD-type murine models and in AD patients (70-78). These observations suggest that early in AD, when levels of A $\beta$  are low, mechanisms amplifying and focusing the effects of A $\beta$  on cellular targets contribute to neuronal dysfunction. Our studies have demonstrated that blockade of RAGE reversed A $\beta$ -induced synaptic dysfunction in AD-affected regions including hippocampus, entorhinal cortex, and visual cortex (17, 19-20). Thus, it appears that RAGE-triggered signal transduction contributes to synaptic dysfunction.

#### 3.4. RAGE and amyloid accumulation in Alzheimer's disease brain

RAGE has been shown to mediate the transport of A $\beta$  through the neuronal cell membrane and the blood brain barrier (7, 22). Administration of sRAGE to animals overexpressing cerebral A $\beta$  significantly reduced A $\beta$  accumulation in the brain. In parallel, A $\beta$  levels were increased in the plasma of sRAGE-treated APP mice. Furthermore, A $\beta$ -sRAGE complex was found in the plasma of those mice (22). These data suggest that sRAGE functions as a decoy peptide: binding to circulating A $\beta$  in the plasma, regulating equilibrium of A $\beta$  between brain parenchyma and the peripheral circulation, thereby enhancing clearance of A $\beta$ .

The role of RAGE-A $\beta$  interaction in exacerbating amyloid pathology was further investigated in transgenic mice overexpressing neuronal RAGE and A $\beta$ . Transgenic RAGE/mAPP mice demonstrated significantly higher A $\beta$  accumulation, as shown by ELISA and quantitative immunohistochemistry for amyloid plaque load in the cortex and hippocampus (39). Importantly, young RAGE/mAPP mice (3-4 months old) displayed functional and pathological evidence of neuronal perturbation, preceding accumulation of cerebral A $\beta$  and plaque formation (19). Recently, Vodopivec reported that there were lower levels of A $\beta$  extractable by SDS and formic acid (insoluble A $\beta$ ) in the brains of RAGE $^{-/-}$ /arcA $\beta$  mice at the age of 6 months, but that this effect disappeared by the age of 12 months (79), suggesting the significance of RAGE in an early stage of amyloid accumulation. However, lack of RAGE did not significantly improve cognitive function in arcA $\beta$  animals using Y maze performance (79). This could be explained by experimental methodologies and animal models. Interestingly, serum levels of A $\beta$ 40 in RAGE $^{-/-}$ /arcA $\beta$  mice were significantly lower than those in the arcA $\beta$  animal at the age of 12 months (79), suggesting a possible relevance of RAGE to A $\beta$  transport across the blood-brain barrier for cerebral A $\beta$  accumulation, though deficiency in RAGE does not affect extracellular amyloid deposits in arcA $\beta$  animal model (79).

Microglia are believed to play an active role in regulating A $\beta$  levels and the amyloid burden in the brain. Overexpression of RAGE in microglia provokes significant increases in A $\beta$  levels in the hippocampus and cortex (8). Fang and colleagues assessed the levels of neocortical and hippocampal A $\beta$  by ELISA in brain extracts prepared from transgenic mice at 5 and 9-10 months of age; at 5 months, levels of A $\beta$  were relatively low in all groups, but these same levels were observed to be significantly higher in mAPP/RAGE mice as compared to single mAPP mice; at 9-10 months a significant increase in A $\beta$  levels was observed in the brains of mAPP mice, but mAPP/RAGE mice displayed significantly more A $\beta$  in the hippocampus and cortex when compared to mAPP mice (8). Introduction of the DN-RAGE transgene into mAPP mice resulted in lower A $\beta$  levels (8). Additionally, in the hippocampus and cerebral cortex of mAPP/RAGE mice, immunoreactive A $\beta$  deposits occupied a larger area and were more extensively distributed as compared to mAPP mice at 9-10 months of age (8). However, the amyloid burden in the hippocampus and cerebral cortex of mAPP/DN-RAGE mice was notably reduced as compared to that observed in both mAPP and mAPP/RAGE mice (8). Studies indicate that the overexpression of microglial

RAGE increases plaque load in animals and that RAGE signal transduction in microglia plays a critical role in amyloid accumulation in the hippocampus and cerebral cortex (8).

It has been suggested that in an A $\beta$ -rich environment, RAGE action favors A $\beta$  accumulation; this could result from increased production of A $\beta$  or from mechanisms preventing its clearance (8). It has been suggested that RAGE-mediated neuroinflammation impairs protective clearance mechanisms, perhaps by sequestering pathogenic A $\beta$  species in an inflammatory environment or down-regulating specific clearance mechanisms (8, 80-81). Since there were no significant differences in hAPP and endogenous mouse APP protein expression among mice carrying mAPP, mAPP/RAGE or mAPP/DN-RAGE transgenes, A $\beta$  accumulation in Tg mAPP/RAGE mice is not simply due to increased hAPP transgene or endogenous APP expression (8). Data from Fang and colleagues suggest that microglial RAGE expression does not significantly affect hAPP transgene expression or A $\beta$  clearance by insulin degrading enzyme, a process that is involved in cerebral A $\beta$  accumulation in mice (82); instead, other RAGE-dependent processes might be involved. An increase in A $\beta$  generation as an indirect effect of microglial mediators affecting neurons or other cell types can not be ruled out (8). RAGE-mediated induction of proinflammatory mediators enhances A $\beta$  accumulation through a positive feedback loop stimulating the RAGE receptor, which further exaggerates neuroinflammation and amyloid pathology (8). These results are consistent with an increasing body of evidence that correlates inflammation with A $\beta$  levels in transgenic mice expressing mutant APP and in AD patients (59, 61, 83). In this context, anti-inflammatory drugs, such as ibuprofen, have been shown to reduce plaque pathology and brain A $\beta$  (61) levels in animal models of AD. Increased induction of proinflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , or interferon- $\gamma$  is also associated with neuronal damage in an A $\beta$  rich environment, as well as A $\beta$  accumulation (8, 19, 50, 81, 84-86). In fact, polymorphisms in the regulatory regions of these cytokines are associated with a higher risk for developing AD (83).

### 3.5. Other RAGE ligands in Alzheimer's disease

Other RAGE ligands might also be associated with pathogenesis of AD. RAGE was initially identified as a receptor for the advanced glycation endproduct (AGE) (87-88). AGE is increased in diabetes, and it also occurs in normal aging and neurodegenerative diseases including AD. Both A $\beta$  and phosphorylated tau, which are key components of AD pathology (amyloid and tau pathology), have been found to be present in non-enzymatic glycation with AGE formation (89-97). AGE modified proteins produce high levels of oxidative stress, increase release of A $\beta$ , and exaggerate neuronal injury (90-92, 97-98).

Endogenous RAGE ligand, S100 could have potential effects on the proinflammatory response in A $\beta$  rich environments. The RAGE ligand S100B can be secreted into the extracellular space where it takes on the role of a cytokine (7). Two other cytokine-like S100 proteins, S100A9 and S100A12, which interact with RAGE and trigger RAGE dependent cellular signaling leading to sustained inflammation, have been identified at elevated levels in the microglia of patients suffering from sporadic AD (7). S100A12 mediates chemotaxis of human peripheral blood-derived mononuclear phagocytes (40). Additionally, in RAGE expressing Bv2 microglia-type cells, S100A12 stimulates production of IL-1 $\beta$  and TNF- $\alpha$  and activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B); such effects are suppressed in the presence of a dominant negative (DN) form of RAGE (RAGE with the cytoplasmic domain deleted) and thus unable to engage in signal transduction (39). Overexpression of S100B in APP mice (Tg2576), one of the AD mouse models, accelerates brain inflammation and neuronal dysfunction as shown by astrogliosis and microgliosis, induction of proinflammatory mediators and AD-like pathology (99-100). Thus, we anticipate that RAGE/S100 interaction might be an important mechanism underlying AD.

## 4. Conclusion

As shown herein, multiple lines of evidence indicate that RAGE is an important cellular target for A $\beta$ -mediated perturbation. A $\beta$  interacts with RAGE on the surface of microglia, neurons, and cells in the vasculature. These interactions exacerbate AD-type pathology including impaired blood brain barrier and vascular function, neuronal stress, activation of microglia and proinflammatory pathways, and deficits in learning/memory in mouse models of Alzheimer's disease. RAGE-dependent signaling in microglia contributes to neuroinflammation and A $\beta$  accumulation, which in turn enhances neuropathological and behavioral changes in the animal models. Blockade of RAGE significantly attenuates A $\beta$ -mediated, sustained neuronal and microglial stress, and improves cognitive and vascular function in AD mouse models (Figure 1). Taken together, the studies described here provide substantial support for targeting RAGE as a therapeutic approach in AD; indeed a RAGE antagonist has already been developed and has demonstrated a protective effect in an animal model (100). The RAGE inhibitor has an excellent safety profile, and has been well-tolerated for over 10 weeks in patients with AD in oral treatments according to results of a Phase II clinical study (102). RAGE inhibitors thus hold a potential for therapeutic advance in halting AD.

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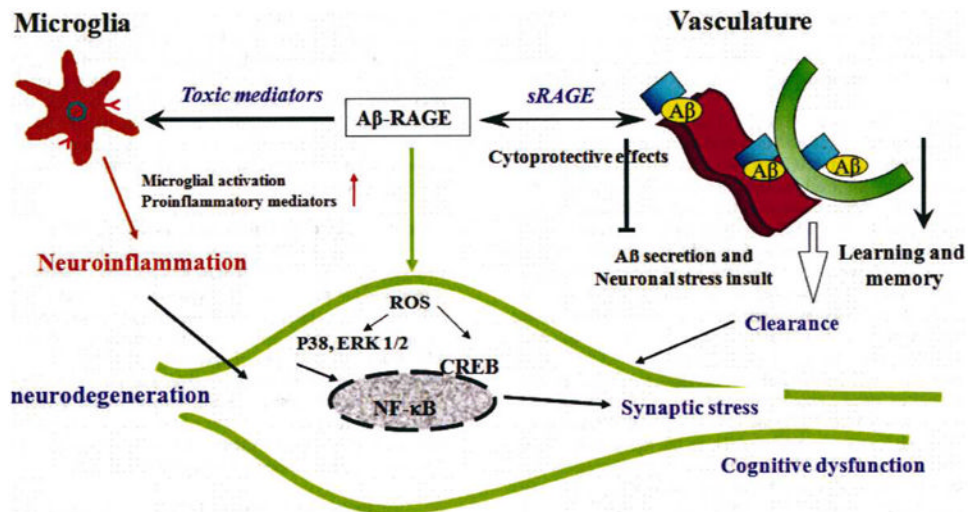


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## Abbreviations

<b>AD</b>	Alzheimer Disease
<b>A<math>\beta</math></b>	Amyloid beta
<b>LTP</b>	long term potentiation
<b>RAGE</b>	receptor for advanced glycation endproducts
<b>MSR</b>	macrophage scavenger receptor
<b>CAA</b>	cerebral amyloid angiopathy
<b>sRAGE</b>	soluble isoform of RAGE
<b>mAPP</b>	mutant form of human APP and A $\beta$
<b>IL-1<math>\beta</math></b>	interleukin -1 $\beta$

<b>TNF-alpha</b>	tumor necrosis factor- alpha
<b>DN-RAGE</b>	signal transduction-defective mutant form of RAGE
<b>MAPK</b>	mitogen-activated protein kinase
<b>ERK</b>	extracellular-signal-regulated kinases
<b>NF-<math>\kappa</math>B</b>	nuclear factor kappa-light-chain-enhancer of activated B cells
<b>TGF-beta</b>	transforming growth factor-beta
<b>ROS</b>	reactive oxygen species
<b>BST</b>	basal synaptic transmission



**Figure 1.**

Evidence of RAGE-mediated cellular perturbation in Alzheimer's brain. Aβ-RAGE interaction exerts its toxic effects on vascular cells, microglia, and neurons. RAGE is involved in Aβ transport across the blood-brain barrier and accumulation of Aβ in brain, leading to a decrease in Aβ clearance and neuronal insults. Inhibition of RAGE-ligand interaction via sRAGE suppresses accumulation of Aβ in brain parenchyma in an AD mouse model. Microglial RAGE interaction with Aβ leads to increased production of proinflammatory mediators and microglia migration/infiltration, which increases neuroinflammation and neuronal damage. Aβ can directly interact with neuronal RAGE and provoke oxidative stress through the generation of reactive oxygen species (ROS) and activation of MAP kinase (P38 and Erk1/2) signalling pathways, subsequently triggering activation of nuclear transcription NF-κB and CREB. Together, these events eventually initiate synaptic and neuronal injury and cognitive dysfunction.