Receptor for Advanced Glycation Endproduct Modulators: A New Therapeutic Target in Alzheimer's Disease

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Abstract

Introduction—Reduction in the deposition of amyloid beta (Aβ) has been the primary target for Alzheimer's disease (AD) therapeutics recently, but in clinical trials this approach has generally been unsuccessful. A common feature of AD pathology is a complex inflammatory component that could be a target for treatment. One feature of this inflammation has been the involvement of the receptor for advanced glycation endproducts (RAGE), whose ligands include advanced glycation-endproduct (AGE)-modified proteins as well as lipids and Aβ, which are found at elevated levels in AD brains.

Areas Covered—Herein, the authors describe the key features of RAGE and how it could have a role in AD pathogenesis. They also summarize the experimental animal and clinical data which demonstrates the therapeutic effect of RAGE inhibition and consider what these findings mean for human disease.

Expert opinion—RAGE has multiple ligands, including Aβ, that are increased in AD brains. Inhibiting RAGE-ligand interactions without activating receptor signaling can reduce multiple pathological pathways relevant for AD. Several RAGE inhibitors and modulators are now being tested as therapeutics for AD. Recent phase II studies have established the good safety and tolerability of TTP448 with some evidence of positive benefit at lower dose. This suggests that further studies are required.

1.0 Introduction

Alzheimer's disease (AD) is the most common form of dementia. Its incidence increases with age and is estimated to affect approximately 4.7 million people in the U.S and 24 million worldwide. With the aging of the population, the total numbers of people affected by AD is expected to increase to 13 million in U.S. and 50 million worldwide by 2030 [1]. The major clinical features of those affected by AD are progressive loss of cognitive function leading to an inability to perform routine activities of daily living. A high percentage of

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residents of nursing homes with dementia have AD and require intensive healthcare services. Looking after AD patients by family members takes a serious toll on health and finances. It is estimated that current annual healthcare costs for AD patients in the U.S are approximately 200 billion dollars.

Current approved treatments for AD are primarily agents that act as acetylcholinesterase inhibitors and function to preserve cholinergic neurotransmissions important for memory functions by slowing down the metabolism of acetylcholine. These drugs, known as donepezil (Aricept), rivastigmine (Exelon) and galantamine (Razadyne), are approved by the Food and Drug Administration (FDA) for AD patients but have effectiveness limited to treating symptoms and likely do not alter the neurodegenerative processes. It has been well appreciated that there is an urgent need for new therapeutic agents, and there have been intensive research to identify new ways of tackling this dreaded disease.

2.0 Alzheimer's disease pathological processes

Understanding what is happening in the brains of AD patients has come from decades of pathological studies of autopsy derived brain tissues of AD subjects [2]. Since the initial observations of Alois Alzheimer of bundles of insoluble structures that become abundant in AD brains, which were subsequently identified as the amyloid plaques and neurofibrillary tangles, preventing their formation has been the primary approach to treating the disease [3].

The pioneering work of Glenner and Wong identified the sequence of the primary amyloid component as 40–42 amino acids of a peptide (defined as amyloid beta (Aβ) peptide) [4]. This was followed shortly afterward by the identification of the amyloid precursor protein (APP) as being the protein from which Aβ is derived; findings that led to the current era of AD research [5]. The pathological features of Aβ were defined in many subsequent studies, which showed that this abnormal protein could be directly toxic to neurons and could also elicit an inflammatory response by microglia, amongst other features (reviews [6, 7]).

There are many abnormal pathological features of AD brains that could be the primary or contributing factor to the selective loss of synapses and death of neurons in brain regions essential for memory and cognition. These include the accumulation of Aβ plaques, the formation of neurofibrillary tangles, activated microglia, reactive astrocytes, complement activation, damage to the cells of the vessels of the brain and leakage of the blood brain barrier, results of increased production of reactive oxygen species, mitochondrial damage, loss of cholinergic receptors, loss of white matter myelinated tracts, abnormal brain glucose transport and metabolism and abnormal cholesterol metabolism [8].

Aβ became the primary focus for reversing the pathological cascade of AD. Based on earlier studies that Aβ could be toxic, the *amyloid hypothesis* for AD was generated. This has been refined in recent years but posits that the abnormal conformations of Aβ, either as beta pleated fibrils or as bioactive soluble oligomers, drives subsequent changes such as the hyperphosphorylation of the microtubule associate protein tau, the abundant feature of neurofibrillary tangles. The incorporation of inflammatory factors into the amyloid

hypothesis came from discoveries that abnormal Aβ could induce proinflammatory changes in microglia, the brain resident macrophages.

Using transgenic mice that develop Aβ plaques due to genetic engineering to include the mutated human APP gene, and then immunized with Aβ peptide to develop an immune response to the peptide, it was shown that plaque develop could be inhibited and memory loss prevented [9]. This spurred the development and testing of similar reagents for use in humans. It was hoped that immunizing humans with Aβ to develop an antibody response or by administering humanized monoclonal antibodies to Aβ would clear the amyloid and therefore slow down or reverse cognitive decline. Although successful in AD model mice, these approaches have not successful in humans due to either life threatening side-effects or simply that they did not prevent cognitive decline even though reduction in Aβ had occurred [10]. Most recent clinical trials with Aβ antibodies have not shown significant benefit [11]. This has raised the question whether simply preventing Aβ accumulation or promoting its removal is the correct therapeutic target. It is likely that there are multiple factors that contribute to the development of AD in addition to Aβ. For example, the strongest genetic risk factor for AD is the apolipoprotein E e4. Possession of this polymorphism of APOE can increase the risk of developing AD by 2.3 to 7 fold, even though the primary role of this protein is as a cholesterol transporter. There are mutations in the APP gene or the presenilin genes that give rise to AD with early onset (<65 years of age). Both types of mutations lead to enhanced production and accumulation of Aβ providing support for the amyloid hypothesis but it needs to be remembered that most AD subjects have no clear genetic cause for the disease.

3.0 Receptor for Advanced Glycation Endproducts – Involvement in AD

The association of the receptor for advanced glycation endproducts (RAGE) with AD came from a gene-screening study showing that RAGE could bind to Aβ in a similar manner as it binds to advanced glycation endproduct (AGE)-modified proteins and ligands [12]. The formation of AGE-modified proteins or lipids result from the non-enzymatic addition of glucose (glycation). This process occurs in the presence of high concentrations of free glucose, a situation present in subjects with diabetes. Although increased levels of AGE-modified proteins have been shown in AD brains [13–15], it is the interaction with Aβ that is considered of greater significance and has been the focus of most subsequent studies. RAGE was identified and cloned from lung tissue and shown to bind to AGE-modified ligands that are abundant in diabetes patients [16]. RAGE activation by AGE modified proteins is considered the primary cause of vascular pathology that occurs in subjects with diabetes [17]. RAGE is expressed by many different cell types, including neurons, brain endothelial cells, astrocytes and microglia. The RAGE protein is composed of three immunoglobulin-like domains; a V-type domain involved in ligand binding, and two C-type domains; one short transmembrane domain and a cytoplasmic tail that is involved in intracellular signaling. The consequence of RAGE ligand interactions was induction of cellular signaling that resulted in increased oxidative stress and increased transcription of proinflammatory genes [18, 19]. The biological features of RAGE are complex as multiple forms of RAGE exist including the cell-associated membrane form of RAGE, which is responsible for pathological signaling, soluble RAGE derived by proteolytic cleavage and release of

membrane RAGE, and endogenous secretory (es) RAGE, a soluble form generated by alternative transcription of the RAGE gene [20, 21]. The soluble forms of RAGE can be protective as they bind up RAGE ligands without activating the damaging proinflammatory signaling. Reduced levels of soluble RAGE in plasma is a feature of AD and early cognitive decline [22].

As mentioned, RAGE was identified as a receptor for AGE-modified proteins and subsequently as one receptor for Aβ, however subsequent studies have shown many additional RAGE ligands, including HMGB1 (Amphoterin), S100B, S100A7, S100A12, S100P, Aβ, integrin Mac-1, and phosphatidylserine [23]. Many of these ligands are also enhanced in AD brains. Due to the diverse nature of RAGE ligands, it became apparent that RAGE was a pattern recognition receptor binding to ligands with particular conformations rather than sequences.

Enhanced RAGE signaling appears to be a feature of chronic inflammation where elevated concentrations of ligands are present. In the presence of these ligands, RAGE expressing cells have increased activation of the nuclear factor kB transcription factor (NF-kB), which not only leads to induction of many inflammatory pathways but also results in increased expression of cell associated RAGE. This feature amplifies the consequence of RAGE activation in producing pathological damage. There is significantly enhanced expression of RAGE in AD disease brains by neurons, microglia, astrocytes and endothelial cells in brain regions with accumulations of Aβ[24–26].

4.0 Experimental Observations on RAGE blocking in AD models

Tissue culture studies with human microglia demonstrated that blocking binding of RAGE to ligand using antibody reagents resulted in reduced inflammatory activation [26]. Key studies were carried out using transgenic mice engineered to overexpress RAGE in neurons [27] or microglia in combination with the development of Aβ plaques [28, 29]. These studies demonstrated enhanced Aβ production, enhanced neurotoxicity and synaptic loss, reduced cognition and enhanced inflammation in mice overexpressing RAGE, while those mice overexpressing a non-signaling form of RAGE did not show these outcomes. It has recently been demonstrated that RAGE activation leads to elevated levels of BACE-1, a key enzyme in the formation of Aβ.

Furthermore, administration of a soluble form of RAGE to plaque developing mice resulted in reduced development of plaques, primarily by binding to Aβ in plasma and preventing its transport across the blood-brain-barrier (BBB) [30]. Essentially the soluble forms of RAGE can bind up ligands such as Aβ and sequester them from cell surface RAGE thus preventing the consequence of RAGE signal activation. This study also demonstrated the role of endothelial RAGE in the transport of Aβ across the BBB from plasma into the brain. Blocking endothelial RAGE reduced the accumulation of Aβ in the brain. An interrelationship concerning the role of RAGE to transport Aβ into the brain, and low density lipoprotein receptor-related protein (LRP) to transport it out of the brain was established [31]. In AD brains, there are increased levels of RAGE on cerebral vessels and decreased levels of LRP [32, 33]; both of which have the effect of promoting accumulation

of Aβ in brain and exacerbating cognitive decline, neurotoxicity and inflammation [31, 34, 35] .

5.0 Pharmacological RAGE inhibitors

Two RAGE inhibitors, TTP488 (formerly called PF-04494700) and FPS-ZM1 have been developed and tested in model studies [34], and TTP488 in human clinical trials. TTP488 is an antagonist of RAGE that blocks its interactions with Aβ (1–42). It can be taken orally and appears to cross the BBB. In a mouse model study of systemic amyloidosis, TTP488 reduced the amount of amyloid in the spleen (27). The manufacturer reported that oral dosing of AD plaque-developing transgenic mice resulted in improved memory and reduced Aβ accumulation (reported as unpublished in [36]).

Another small molecule antagonist of RAGE (designated FPS-ZM1) has been developed and tested in experimental models. This agent targets the V type domain of RAGE preventing Aβ binding and RAGE activation [37]. It appears to have positive pharmacological properties as it can cross the blood brain barrier and not prevent Ab binding to LRP. Treatment of plaque developing mice with FPS-ZM1 reduced influx of Aβ into the brain, and in brain significantly reduced BACE-1 levels in treated plaque developing mice and reduced microglia expression of proinflammatory cytokines. The activity of FPS-ZM1, which can cross the BBB, was significantly greater than the analogy FPS2, which does not. Both agents prevented Aβ influx into brain, but FPS-ZM1 was more effective at lowering events occurring in the brain such as BACE-1 expression, neuroinflammation and cerebral plaque load [37]. This agent was also effective at preventing hypertension induced exacerbation of AD pathology mediated by RAGE activation of cerebral endothelial cells [38].

6.0 Human Clinical Trials of RAGE Inhibitors/Modulators

Phase 1 and Phase 2 clinical trials have now been carried out with human subject to test the safety and efficacy of TTP488. In the phase 2a trial, three groups of subjects were examined using two doses of TTP488 and a placebo for 10 weeks [36]. The subjects were patients with mild to moderate AD with average age of 75 years. Twenty seven subjects received low dose of TTP (30 mg/day for 6 days followed by 10 mg for the remaining time) and 28 subjects received the high dose (80 mg/day for 6 days followed by 20 mg for the remaining time) with 12 participants as placebo. Completion of treatment was seen in 88.9% of participants at the low dose, 85.7% of those at the high dose and only 66.7% of the placebo group. The doses appeared to be well tolerated with no significant difference in adverse effects between the high and low dose subjects. The treatments did not show any differences in plasma Aβ levels, inflammatory biomarkers or cognitive measures but generally showed that the agent was well tolerated [36] Indeed, at week 10 the placebo groups improved of +1.1 ± 0.6 points on MMSE while those on TTP448 30/10 mg and 60/20 mg worsened by 0.6 ± 0.4 and 1.2 ± 0.6 points, respectively. Similarly, on ADAS-Cog, the placebo-treated patients worsened by 1.6 ± 1.4 points, but the TTP448-treated patients worsened more rapidly (3.1 ± 0.9 and 2.2 ± 1.0, respectively)[36].

As a result of the phase 1 trial, a larger multi center 18 months phase 2 trial of TTP448 (PF-04494700) was carried out with 399 participants to determine if there was evidence of effectiveness in slowing cognitive decline[39,40]. In this larger trial, 135 enrollees were assigned to the high dose group that consisted of 6 days at 60 mg/day followed by daily doses of 20 mg/day for up to 6 months; a lower dose of 20 mg/day for 6 days followed by 5 mg/day for up to 18 months and 132 participants on placebo medication. The primary cognitive assessment criteria were the Alzheimer's disease Assessment Scale Cognitive (ADAS-cog) test. The high dose treatment was discontinued at 6 months due to significant worsening in cognitive measures and also increased confusion and falls. These adverse effects were not observed in the low dose or placebo groups. The study showed a high dropout rate with only 11 of 132 remaining on low dose treatment for the complete 18 months period; however 69 subjects treated for a period with low dose TTP448 completed cognitive assessment at 18 months. This group showed a reduced change in ADAS-cog score compared to placebos, while screened subjects who had been on high dose treatment were equivalent to the placebo group. In a small group of subjects sampled at 12 months, there were no significant differences in CSF biomarkers of Aβ, tau and phosphotau between the treatment groups. It is not known if the reason for the adverse but reversible increase in cognitive decline in the high dose group was due to specific RAGE inhibition effects or off-target effects.

Further analyses of the low dose treatment group were carried out to include measurements of plasma concentrations of TTP448 on samples taken at successive 3 month intervals [39]. Changes in ADAS-cog varied depending on the plasma concentrations of TTP448. Subjects who had TTP488 concentrations in the lowest 40% (0.1–16.75 ng/mL) had a significant difference on their ADAS-cog values than the placebo group (−2.7 score p<0.03) indicating a beneficial effect on reversing cognitive decline. However, those subjects who had concentrations in the range 46.8–167.7 ng/mL had ADAS-cog values equivalent to the placebo group. The benefits of the low dose of TTP448 were greater in patients with mild AD compared to those with moderate AD. The results of this analysis suggest that a lower dose of TTP488 around 5 mg/day would have a positive effect in slowing down cognitive decline as compared to placebo. To confirm this, another trial using the 5 mg/day dosage would need to be performed [40].

7.0 Conclusion

The pathological consequences of activation of RAGE by ligand(s) have been established in a wide range of experimental models, including those that are investigating AD. The result of RAGE activation is generally deleterious resulting in enhanced oxidative stress, inflammation and vascular dysfunction as well as altered Aβ trafficking, all of which are involved in AD. As animal models of AD have shown significant therapeutic benefit of blocking RAGE activation, it is a reasonable target for human AD drug development. Clinical trials of a first generation agent TTP448, a small molecule antagonist of RAGE have produced some promising results. It appears to have a narrow therapeutic effective dose, but low dose of this agent produced significant reduction in cognitive decline. As such further trials are warranted of this agent. In addition, a newer generation agent that has shown effectiveness in AD animal models is available for human trials.

8.0 Expert Opinion

AD is likely multifactorial in etiology. All previous anti-amyloid therapies have been similarly palliative at best and harmful at worst, and these compounds are likely no exception. It should make one question whether or not an anti-amyloid strategy is actually the correct strategy.

Treating AD patient with agents that were designed to prevent Aβ accumulation or aggregation, including immunotherapy approaches using vaccines or antibodies or anti-aggregation agents, such as tramiprosate, have failed to show clinical efficacy and in some cases have had serious side effects. With repeated failures, the amyloid hypothesis itself has been called into question [41]. First, is it the wrong target altogether. Second, is the synchrony of amyloid deposition preceding symptoms mean we should be treating with anti-amyloid treatments in the pre-symptomatic phase? Third, should symptomatic treatments be focused on non-amyloid based treatments (tau, excitotoxicity, etc)? Fourth, should we reconsider if it is reasonable to tie biomarker outcomes to clinical outcomes?

RAGE is involved in multiple potential pathological that could contribute to AD pathology, including Aβ transport, oxidative stress, inflammation and neurotoxicity. The key finding in this area of research is the RAGE is a chemo-attractant to Aβ and is directly mechanistically related to AD pathogenesis. Additionally, RAGE and AGEs have been implicated in diabetes. RAGE and AGEs could be one of the mechanistic ties between AD and DM. Inhibiting RAGE has been shown to have significant therapeutic benefit in AD disease models. RAGE inhibition offers the potential of reducing multiple factors not just Aβ accumulation. However, RAGE inhibitors, if they are truly another anti-amyloid target, could be prone to the same vulnerabilities insofar as anti-production and anti-clearance strategies of Aβ have not materialized in robust clinical benefit.

One inherent appeal of RAGE inhibitors over other anti-amyloid treatments is the oral administration of the drug. This could supplant the current IV administration route of other anti-amyloid treatments. Another appeal is multiple mechanisms that RAGE inhibitors could be target include aggregation and inflammation. Two small molecule RAGE antagonists are available and are at different stages of development. We have been involved in trials with TTP448, a first generation agent, in human AD subjects. This agent appeared to have a narrow therapeutic window, but the low dose showed promising beneficial effect at slowing cognitive decline. At odds is the potentially conflicting data coming out of the phase IIa study. Specifically, the study met the pre-specified futility endpoint but when followed to study end, subjects treated with TTP488 were significantly better on the ADAS compared to subjects treated with placebo. Hotly debated is whether to interpret these data as positive or negative.

Further trials of this or similar agents are warranted, though biomarker measures are needed to assess how these agents affect the properties of soluble forms of RAGE, the naturally occurring RAGE inhibitors. A phase III study is planned. Confounding this and all anti-amyloid treatments will be interpretation of biomarker outcome data.

Much is unknown about this approach. First, does an anti-RAGE approach result in reduction of amyloid on PET imaging? Second, is the likely benefit mediated through improvement on metabolic activity? Third, CSF biomarkers have not been looked at in detail. How could CSF inform us on mechanism of action? Finally, how should a potential clinical benefit be interpreted if no biomarker change is identified? More studies will be needed to add to the growing body of evidence that this is an attractive therapeutic target in AD pharmacotherapy.

Acknowledgments

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Article Highlights

There is a critical need to develop new ways of treating Alzheimer's disease

Treatments focused primarily on inhibiting Aβ accumulation and aggregation have not been successful in clinical trials

The damage in the AD affected brain reflect the outcome multiple different pathologies besides the toxicity of Aβ

Aβ is a ligand for the pattern recognition receptor RAGE

Activation of RAGE by Aβ has multiple pathological consequences

Inhibiting RAGE-Aβ interactions is effective in reducing pathology in AD mouse models

Recent clinical trials with TTP448, a small molecule RAGE antagonist have shown some clinical effectiveness at a lower dose, but adverse effects at higher doses

A newer generation RAGE antagonist (FPS-ZM1) has shown effectiveness in a mouse AD model