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REVIEW ARTICLE

Receptors for Advanced Glycation End Products (RAGE): Promising Targets Aiming at the Treatment of Neurodegenerative Conditions

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Abstract: Advanced glycation end products (AGEs) are compounds formed after the non-enzymatic addition of reducing sugars to lipids, proteins, and nucleic acids. They are associated with the development of various clinical complications observed in diabetes and cardiovascular diseases, such as retinopathy, nephropathy, diabetic neuropathy, and others. In addition, compelling evidence indicates that these molecules participate in the progression of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Multiple cellular and molecular alterations triggered by AGEs that could alter homeostasis have been identified. One of the main targets for AGE signaling is the receptor for advanced glycation end-products (RAGE). Importantly, this receptor is the target of not only AGEs, but also amyloid β peptides, HMGB1 (high-mobility group box-1), members of the S100 protein family, and glycosaminoglycans. The activation of this receptor induces intracellular signaling cascades that are involved in pathological processes and cell death. Therefore, RAGE represents a key target for pharmacological interventions in neurodegenerative diseases. This review will discuss the various effects of AGEs and RAGE activation in the pathophysiology of neurodegenerative diseases, as well as the currently available pharmacological tools and promising drug candidates.

Keywords: AGEs, neuroinflammation, neurodegeneration, drug development, RAGE, Alzheimer's disease, Parkinson's disease, oxidative stress.

1. INTRODUCTION

The chronic loss of neuronal structure and function, leading to neuronal death, is a hallmark of neurodegenerative diseases, a group of pathological conditions that represent a heavy burden to the health care systems worldwide [1]. The underlying causes of the majority of these diseases are still unknown. Since mitochondrial dysfunction, oxidative stress and neuroinflammation are common biochemical and cellular alterations of these diseases [2, 3], they represent promising targets for developing new therapeutic agents to halt the progression of these conditions.

Advanced glycation end products (AGEs) are characterized as a group of biomolecules formed by irreversible non-enzymatic glycation of proteins by reducing sugars, *e.g.*, the carbohydrates obtained from the diet. The formation and accumulation of AGEs, consequently linked to the biochemical signaling pathways with which they are associated, might contribute to several complications commonly found in diabetic patients, such as vascular damage, kidney failure, and nerve degeneration [4-6]. Taken together, these events might contribute to the development of complex neurodegenerative scenarios, such as Alzheimer's disease (AD) and vascular dementia [6, 7].

The present review focuses on the biochemical steps associated with AGEs formation in biological tissues. Then, we describe the endogenous receptors for AGEs and the consequences of their activation for neuronal processes, both in cellular and tissue milieus. Finally, we describe the potential pharmacological interventions of mitigating AGE content and RAGE activation as promising treatments for neurodegenerative diseases.

2. THE CHEMISTRY OF AGES FORMATION

A generic biochemical pathway leading to the formation of AGEs is represented in Fig. (**1**). The described steps are

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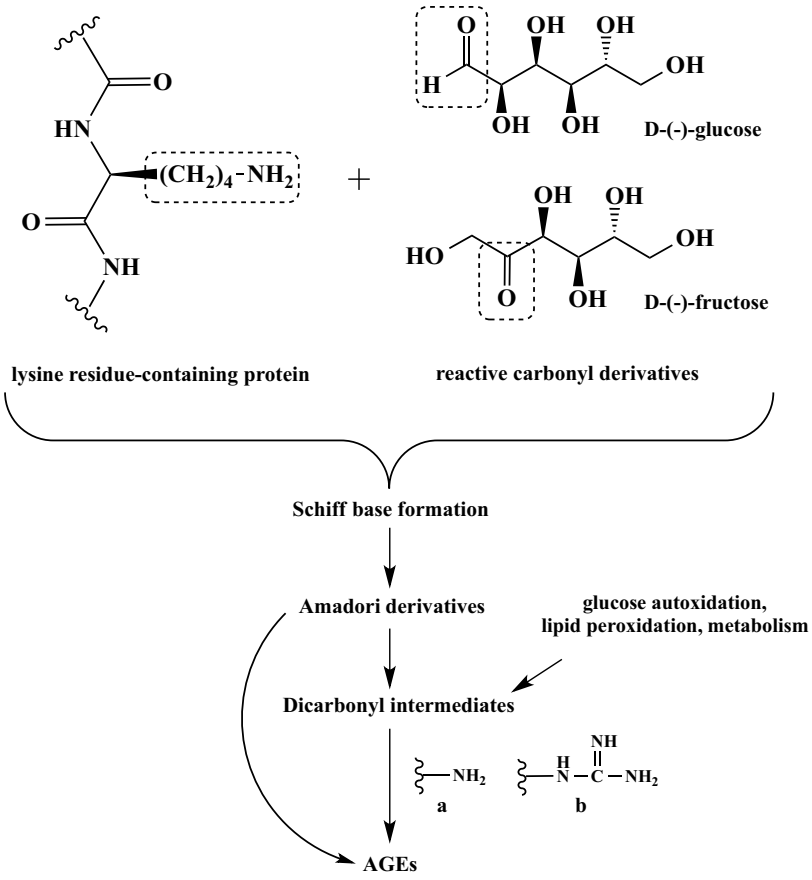

Fig. (1). Generic *in vivo* biochemical pathway resulting in the formation of AGEs. Arginine and lysine residues in proteins and carbonyl compounds provide amines and ketone/aldehyde (groups in dashed lines) to Schiff base formation and subsequent reactions. **a** and **b** represent lysine and arginine residue-containing proteins, respectively, which react with dicarbonyl intermediates, also yielding AGEs.

firstly based on a condensation reaction between amine or guanidino groups, usually represented by side chains of lysine and arginine-containing proteins, with carbonyl compounds, including aldohexoses and ketohexoses, such as glucose and fructose, respectively, as well as α-dicarbonyl moieties derived from autoxidation processes, lipid peroxidation and glycolysis [5, 8, 9]. The sequential steps, which lead to AGEs as final products, have been extensively discussed in the literature [10-13] since the first non-enzymatic browning observations described in 1912 by Maillard [14].

The first reaction, which must be highlighted in the AGEs cascade, is characterized by a Schiff base formation (Fig. **2**). Schiff bases are organic compounds (Fig. **2A**) displaying a C=N bond (imine) as their most important feature. These compounds were firstly obtained by Hugo Schiff in 1864 from his observations based on reactions involving aldehydes and amines, such as aniline [15]. In the last decades, many pathways and experimental conditions have been explored based on a plethora of imine derivatives [16-18], including reactions and compounds presenting a wide range of applications in biology, pharmacology, and medicinal chemistry [19-32].

The relevance of Schiff base formation in biochemistry is also well-represented by crucial steps in metabolism, such as pyridoxal-dependent metabolic pathways. Pyridoxal is an aldehyde presenting vitamin B6 activity, daily obtained from different dietary sources, including cereals, vegetables, fish, and pork [33-35]. Pyridoxal phosphate (PLP), the active *in vivo* form of pyridoxal, is the cofactor of several enzymes related to the transamination of amino acids [36-38], the formation of neurotransmitters [34, 39] and the biotransformation of drugs [40-42]. The cofactor activity of PLP is dependent on the formation and the hydrolysis of imine bonds with enzymes, as shown in Fig. (**3**) for aspartate aminotransferase.

The equilibrium between the imine bond formation and the hydrolysis of Schiff bases is represented by the mechanism in Fig. (**2B**) and depends on factors, such as pH values and the concentration of amines and carbonyl compounds [43-45]. Once the equilibrium towards C=N bond formation is favored, the subsequent and irreversible formation of Amadori and dicarbonyl derivatives may be driven, leading to final AGEs formation (Fig. **1**). In the case of AGEs, the increase of carbohydrate consumption by a subject may be a way to increase the production of AGEs in its organism. Fig. (**4**) shows the structures of common and well-characterized AGEs.

3. RECEPTORS FOR AGEs (RAGE): STRUCTURAL FEATURES AND SIGNALING ASPECTS

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin superfamily. The ligand-receptor binding occurs in different regions (V, C1, and C2) of the extracellular domain of RAGE, also known as soluble

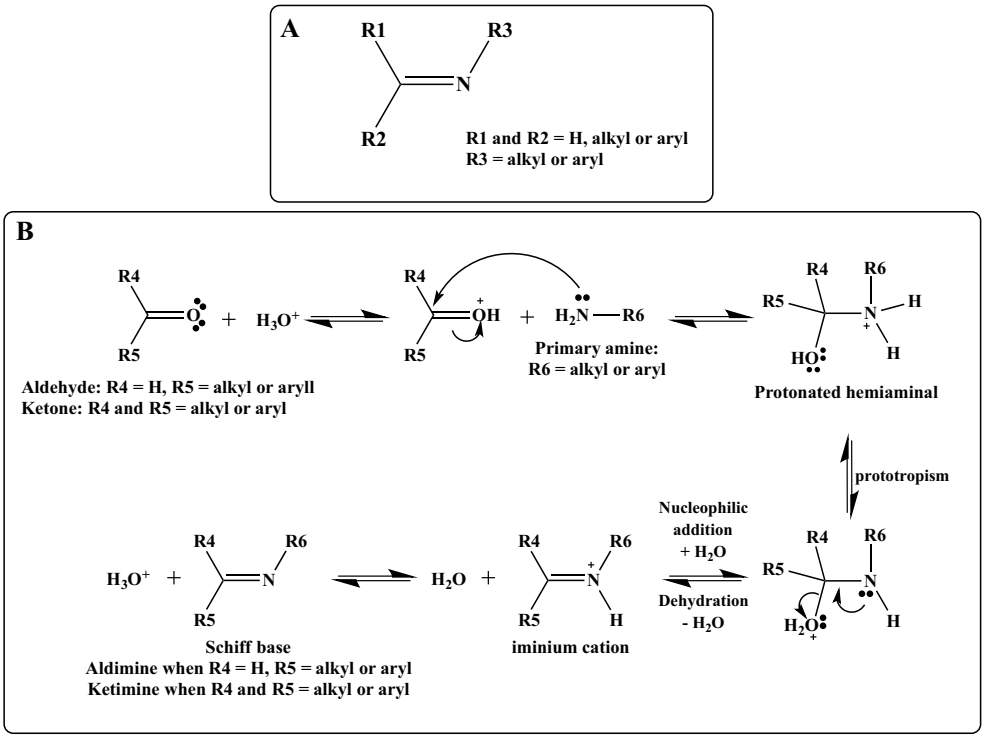

Fig. (2). **A**) General structure of Schiff bases; **B**) Proposed mechanism of Schiff bases formation. Aldimines are Schiff bases formed by the condensation of aliphatic or aromatic amines with aldehydes, releasing H_2O. Similarly, ketimines are Schiff bases formed by the condensation of aliphatic or aromatic amines with ketones, also releasing H_2O. Schiff bases can form their precursors through iminium cation formation in acidic conditions, leading to the hydrolysis of the C=N bond.

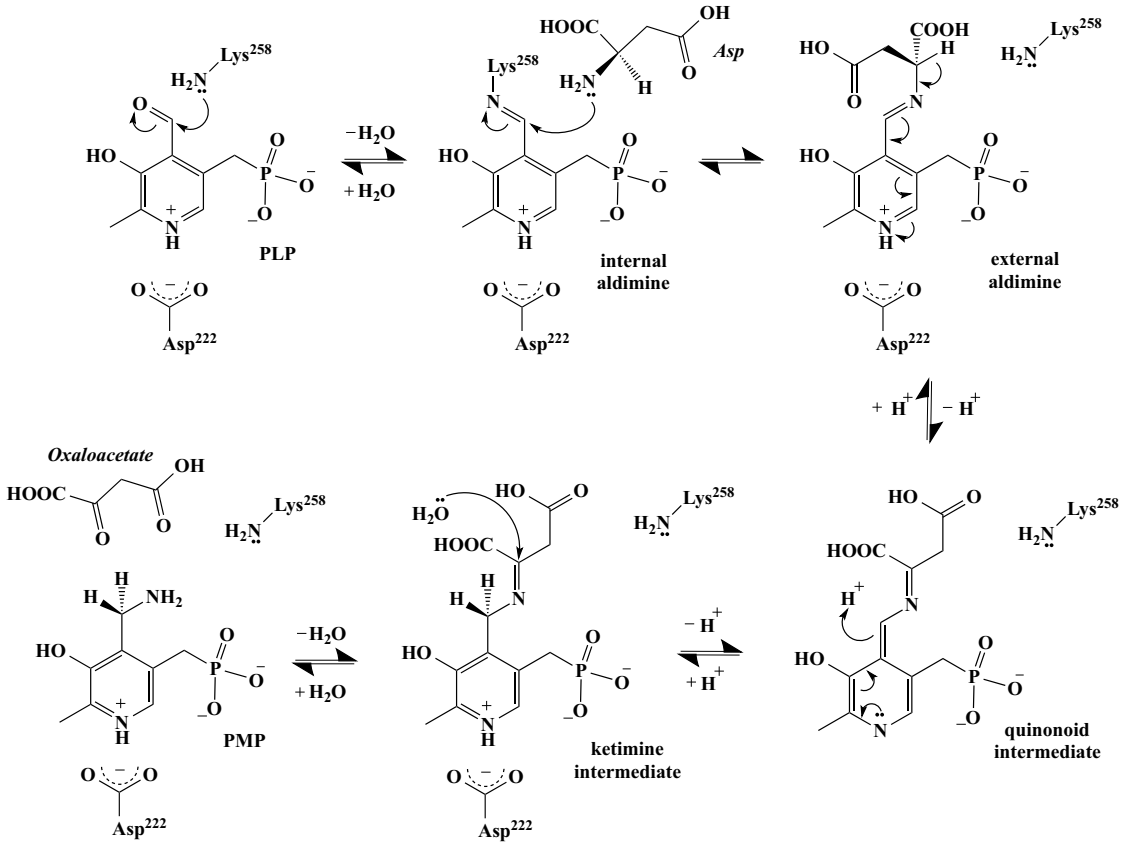

Fig. (3). Adapted mechanism of aspartate (Asp) deamination step in oxaloacetate, catalyzed by aspartate aminotransferase-PLP complex, which is converted into the aminotransferase-PMP complex. Asp222 and Lys258 represent residues of aspartate aminotransferase. PLP (pyridoxal phosphate) and PMP (pyridoxamine phosphate) are cofactors [37].

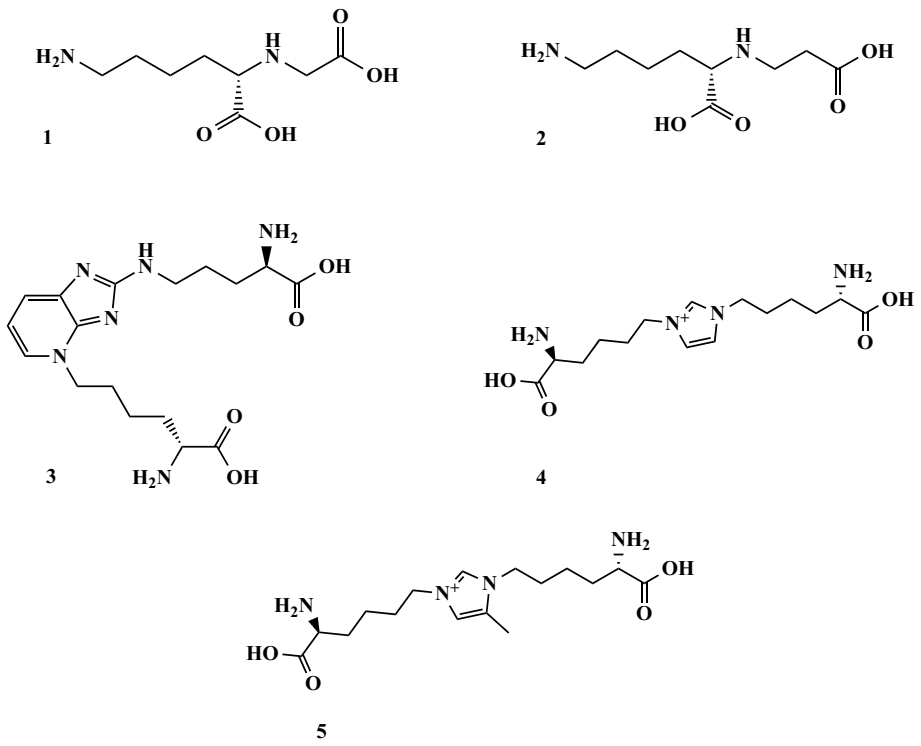

Fig. (4). Common AGEs: n-carboxymethyllysine (1), carboxyethyllysine (2), pentosidine (3), glyoxal-lysine dimer (4), and methylglyoxal-lysine dimer (5).

RAGE (sRAGE), although the majority of ligands interact with the variant (V) part of the receptor [46-51]. The most relevant ligands of this receptor are represented by AGEs, glycosaminoglycans, high-mobility group box-1 (HMGB-1), members of the S100 protein family, and the amyloid β peptide (Aβ).

With regards to structural features, the extracellular binding domains of RAGE are rich with lysine and arginine residues, providing a positive net charge that interacts better with ligands that might present an overall negative charge [50], such as n-carboxymethyl lysine (**1**, Fig. **4**) and carboxyethyl lysine (**2**, Fig. **4**). These ligands are also two major AGE structures found in relatively high concentrations in tissues.

The binding activity of more complex amino acid-derived structures to the extracellular binding domains of RAGE has also been investigated. The high mobility group box-1 (HMGB-1; also known as amphoterin) and its isoforms [47] are important examples in this context. During inflammation, HMGB-1 is secreted mostly by monocytes [52], and the main cellular consequence of HMGB-1/RAGE interaction is the regulation of cell motility. Similarly, Aβ binding to RAGE mediates the neurotoxicity through oxidative stress and microglial activation [53]. More importantly, the interaction of this peptide with this receptor in endothelial cells increases the transport of Aβ across the blood-brain barrier and the expression of proinflammatory cytokines. Consequently, it could, in turn, contribute to the accumulation of Aβ in the brain parenchyma [54].

In the intracellular domain, RAGE directly interacts with the Diaphanous-1 (Dia-1) protein upon ligand binding, and this interaction is responsible for the initiation of the downstream signaling cascades that follow receptor activation [55]. The mitogen-activated protein kinase (MAPK)-ERK1/2 pathway is one of the pathways responsible for controlling gene expression, cell migration, and cytokine secretion [56]. Different ligands may trigger different signaling pathways, which are determined by the nature of the ligand that is responsible for RAGE activation through extracellular binding domains [57]. Other intracellular proteins, such as the Rho family small G-proteins and cdc42/Rac, are also downstream targets that may account for the RAGE-mediated pathogenesis of inflammatory disorders and tumor growth/metastasis [56]. Indeed, RAGE regulates transcription through several signaling pathways that profoundly impact cell behavior [57].

The signaling pathways activated by RAGE are involved in many molecular and cellular events, including the alteration of gene expression, cellular migration, and cell death [57]. The effects of changes on the expression of RAGE and their related signaling pathways have been investigated in animal models. RAGE knockout mice revealed hyperactivity as well as higher sensitivity to auditory signals [58]. Furthermore, the modulation of the receptors has been described to contribute to neurite outgrowth, nerve regeneration, and neuronal differentiation [59, 60]. Similarly, inhibition of the RAGE signaling increased the survival rates in animal models of sepsis [61]. Moreover, the activation of RAGE by its ligands further activates the nuclear factor (NF)-κB and MAPK signaling pathways, major players in inflammation, leading to significant modulation of the innate immune response in sepsis [62] and neurodegenerative diseases [63]. Interestingly, similar pathways are activated by well-known

receptors involved in immune responses, such as the Toll-like receptors.

There is positive feedback in the RAGE signaling since activation of this receptor further activates NF-κB, which, in turn, increases RAGE expression. Thus, although its expression is low in the tissues, it can be augmented by increased levels of AGEs [64, 65]. This could be important in situations like diabetes and cardiovascular conditions since high AGEs concentration and RAGE activation have been suggested to correlate with vascular stress and atherosclerosis aggravation [66].

4. ROLE OF AGEs IN NEURONS, MICROGLIA AND ASTROCYTES

RAGE is expressed in neuronal cells [67] and other cell types [68]. This receptor has physiological roles in these cells, such as the involvement in neurite outgrowth during development [47, 60]. It has been demonstrated that S100B and HMGB-1 are important factors in young and adult neuronal differentiation, both in the central and the peripheral nervous systems, impacting processes, such as neurite outgrowth and elongation observed in the cerebellum and peripheral nerves [47, 59, 69-71]. Interestingly, Meneghini and collaborators found that a localized expression of RAGEs in the undifferentiated neural stem/progenitor cells of mouse adult subventricular zone (SVZ) plays an important role in proliferation and neuronal differentiation upon ligand binding, and that this event is dependent on NF-κB activation [72]. More evidence from the same research group suggests that RAGE activation by Aβ 1-42 oligomers and by HMGB-1 possibly promotes neuronal differentiation in hippocampal neural progenitor cells through the RAGE/NF-κB signaling pathway [73]. Although this proneurogenic role of RAGE activation may suggest a beneficial effect in AD, these data must be interpreted with caution. Since the authors did not observe any difference in the number of $BrdU^+/NeuN^+$ cells of transgenic in comparison to WT mice, they propose that this proneurogeneic effect of RAGE activation is insufficient to restrain the neurodegenerative course of the disease. Besides, even though these new neurons are formed, they could not be matured or integrated due to the unfavorable environment. This complexity highlights the importance of persistent investigations related to the molecular and cellular mechanisms involving RAGE activation. A better understanding of the process would culminate in providing pharmacological tools aiming at the modulation of a sustained hippocampal neurogenesis process, consequently paving the way for potential treatments of neurodegenerative disorders.

Although the apparently positive physiological roles of RAGE activation by different ligands are promising mechanisms in neurogenesis, early *in vitro* studies demonstrated the neurotoxicity of the AGEs [74-77]. Upon interactions with their ligands, RAGE activation triggers oxidative stress and the activation of NF-κB transcription factor in neurons [78]. In parallel, the RAGE expression may increase during aging, preferentially in glutamatergic pyramidal neurons of the cerebral cortical layers [79], which could contribute to neurodegeneration [80]. Indeed, RAGE-positive granules were identified in the brain of patients with AD [80].

The microglia also express RAGE, which, once stimulated, induces cell activation [81, 82]. S100B activates RAGE in microglia [83], and the extracellular domain of these receptors is involved in reactive oxygen species (ROS) generation and subsequent activation of the nitric oxide synthase (NOS), leading to the release of nitric oxide [84]. Furthermore, this RAGE ligand activates NF-κB [83, 84] and upregulates cyclo-oxygenase 2 (COX-2), an important enzyme involved in the production of prostanoids [85]. Further studies have demonstrated that AGEs activate these cells and induce additional pathways, such as extracellular signal-regulated kinases (ERK1/2) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), leading to the production of different inflammatory mediators [86-91]. Finally, AGEs can lead to microglia activation by indirect pathways as well. The RAGE binding is supposed to directly increase blood-brain barrier (BBB) permeabilization by Aβ modulation [92-94], followed by microglia activation with the production of toxic cytokines and chemokines.

A study using transgenic mice (Tg) expressing mutant human APP (mAPP) in neurons and RAGE in microglia demonstrated that the overexpression of the receptor increases neuroinflammation, shown by the increased levels of interleukin (IL)-1β and tumor necrosis factor (TNF)-α, Aβ accumulation, and the accelerated impairment of spatial learning/memory [95]. Interestingly, mhAPP mice with an insertion of a dominant-negative RAGE in microglia revealed behavioral and synaptic improvement in comparison to mhAPP mice [96]. Finally, activated microglia induce the production of AGE-albumin, which could lead to neuronal death [97].

Similar to neurons and microglia, it has also been demonstrated that astrocytes express RAGE [98]. Wang *et al.* [99] demonstrated that the incubation of cultured astrocytes with two glycated forms of albumin, Glu-BSA and Gal-BSA, induces the release of IL-1β and TNF-α by the cells in a dose-dependent manner, suggesting that astrocytes, in the presence of elevated concentrations of AGEs, might contribute to the inflammatory state of the neuronal tissue. AGE-activated astrocytes also could increase BBB permeability and, by extension, lead to the production of vascular endothelial growth factor [100]. Therefore, it is possible that the increase in RAGE expression might induce the synthesis and the release of proinflammatory mediators, probably inducing the disruption of the BBB functions [98].

Pyramidal neurons and astrocytes evaluated by immunohistochemistry techniques in patients with AD show AGE accumulation and colocalization with amyloid plaques, caspase-3 and the neuronal nitric oxide synthase (nNOS) enzyme, which are known as molecular markers of cellular death [101]. Additionally, astrocytes have demonstrated a RAGE-mediated phagocytic ability to engulf Aβ [102]. Indeed, astrocytic RAGE can interact with other ligands, such as S100B, and this binding can be antagonized by pentamidine, an antiprotozoal drug. Pentamidine reduces the signs of reactive gliosis, also decreasing RAGE expression in astrocytes. The drug also reduced proinflammatory mediator levels, thus reducing neuroinflammation. Moreover, pentamidine displayed a neuroprotective effect on CA1 pyramidal neurons [103]. The prolonged exposure to RAGE ligands or

abnormally increased concentrations of some types of AGE may induce the appearance of reactive astrocytes involved in the development or progression of neurodegenerative disorders [104].

As previously mentioned, RAGE has different roles in cell types in the brain. Various effects are deleterious, such as increased production of inflammatory mediators, oxidative stress and glial activation that could lead to BBB disruption, neuroinflammation and neurodegeneration. Thus, their role in the pathogenesis of neurodegenerative diseases is possible. In the next sections, we will discuss the roles of these receptors in neuropathologies.

5. ADVANCED GLYCATION END PRODUCTS IN NEURODEGENERATIVE DISEASES

5.1. Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and neurodegenerative disease [105]. It is characterized by cognitive decline, progressive loss of memory, speech, and the ability to recognize people and objects [106, 107]. Aβ plaques and neurofibrillary tangles are two important hallmarks of AD [108]. The progression of the dysfunction involves the degeneration of neurons in specific regions, such as the entorhinal cortex, hippocampus, and cortical and subcortical areas [109]. It is estimated that more than 90% of AD patients are sporadic with a late onset of the disease [110], while 2-5% of patients have an earlier onset [111]. Genetic factors associated with AD are assumed to be the mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2), and the expression or polymorphism of ε4 allele of apolipoprotein E (APOE) [111-113].

Recent reports suggest that AGEs contribute to the development and progression of AD [114-116]. Higher levels of AGEs were identified in the brain of AD patients in comparison to controls [117]. These compounds might be involved in cognitive decline through β -amyloid deposition and plaque formation [118]. Intracerebroventricular injection of HMGB-1 in WT, $TLR4^{-/-}$, and $RAGE^{-/-}$ mice induced memory impairment in the novel object recognition test. However, a pharmacological blockade of TLR4 in $RAGE^{-/-}$ mice abolished the effect of HMGB-1 [119], suggesting an important role of the pattern recognition receptor in the deleterious actions of the RAGE ligand.

It was proposed that AGEs induce tau hyperphosphorylation in SK-N-SH cells, primary hippocampal neurons, and rat brains through the RAGE/glycogen synthase kinase (GSK)-3 pathway [120-122]. This finding was confirmed by immunohistochemical evidence showing early neurofibrillary tangles formation and neuronal degeneration [118, 123]. According to these results, the disruption of RAGE-ligands binding might emerge as a promising approach aiming at the treatment of AD, potentially interrupting or decreasing progressive neurodegeneration.

The AGEs-RAGE binding is supposed to contribute to cognitive impairment by synaptic and neuronal dysfunction [123], as well as mitochondrial dysfunction and energy metabolism alteration [124]. Mice fed with methylglyoxal-BSA (1.33%), which is considered an AGE-enriched diet, revealed increased ROS levels, and reduced mitochondrial activity in the brain, as well as impaired learning and memory scores in comparison to animals subjected to a normal diet [114]. Moreover, the db/db diabetic mice have increased RAGE expression in the hippocampus and presented a significant cognitive decline in the Morris water maze model. These pathological events were reduced by liraglutide administration *via* the downregulation of RAGE [125]. Thus, one could speculate that dietary AGEs could, in the long-term, be responsible for metabolic diseases that, in turn, lead to neurodegenerative processes.

Many studies have suggested that RAGE can regulate Aβ neurotoxicity [93, 123, 126], either by playing a role in the production of the peptide or failure of its clearance [123]. RAGE expression is elevated in the areas where Aβ is deposited [127]. The interaction of RAGE with Aβ leads to oxidative stress due to the activation of inflammatory signaling pathways with elevated production of ROS [54]. However, it is still unclear how this interaction occurs and its function in AD patients.

Double transgenics (mutant APP (mAPP)/RAGE) mice displayed impaired learning and memory and altered synaptic plasticity markers in comparison to mAPP transgenic mice [128]. Similarly, transgenic mice that express mAPP in neurons and RAGE in microglia presented a decrease in AChE activity and disruption of learning and memory [129]. In a more recent study, the deletion of RAGE in mAPP mice reduced beta and gamma secretase activity, as well as Aβ production, which was accompanied by attenuation in learning/memory impairment. These benefits might also be linked to the reduction in the activity of GSK3β and p38 MAPK [130]. Thus, Aβ/RAGE-induced neuronal disturbance in AD is a promising pharmacological target.

Similar to the higher levels of AGEs observed in the brains of AD patients, the expression of RAGE is also increased in these tissues in comparison to non-demented individuals. Interestingly, the incubation of microglia, isolated from the brains of both groups, with Aβ, led to an increase in M-CSF production, which was more pronounced in the cultures obtained from the patients. The addition of anti-RAGE $F(ab')_2$ antibodies reduced the levels of this cytokine [87]. RAGE levels in the brain were also correlated to the severity of the disease as determined by the Braak staging [87, 131].

The mechanisms involved in the pathogenesis of AD are still not completely clear. However, it is important to note that various pathogenic effects mediated by Aβ in the disease require activation of RAGE, making this receptor a pharmacological target for the therapeutics of AD.

5.2. Parkinson's Disease

Parkinson's disease (PD) affects approximately 1.5% of individuals over 60 years old worldwide, and it is the second most prevalent neurodegenerative disease [132]. Both motor symptoms, such as rest tremor, rigidity, bradykinesia and postural instability, and non-motor symptoms, including anxiety, depression, cognitive decline, pain and many others, may occur [133]. The neuronal cell loss in the SNPc, the presence of Lewy bodies, and the abnormal aggregation of the protein α-synuclein are common pathological features in PD [134, 135].

Under *in vitro* conditions, it was shown that the cluster AGE-α-synuclein aggregates in a different conformation in comparison to the normal α-synuclein. This structure binds with DNA and alters its secondary conformation and integrity [136]. In an animal model of PD, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced RAGE expression, and the deletion of this receptor reduced the cell death induced by neurotoxin [137]. This positive regulation of RAGE has also been demonstrated in a study that evaluated the effects of vildagliptin in the rat rotenone PD model [138]. The same was not observed by Viana *et al.* [139], who found no alteration in S100B levels and RAGE expression in an animal model of MPTP.

Increased AGE expression levels in the substantia nigra, amygdala, and frontal cortex, and increased RAGE expression in the substantia nigra and frontal cortex were observed in the early stages of PD patients compared to healthy controls [140]. Münch *et al.* [141] demonstrated that AGEs are present in Lewy bodies early in the human brain, promoting early changes, such as the involvement in protein crosslinking and formation of insoluble, non-degradable aggregates rather than late phenomena of PD. A recent clinical study suggests that PD patients have higher plasma levels of carboxymethyl lysine, compared to healthy individuals [142]. Moreover, RAGE can interact with S100, activating the NF-κB and TNF-α signaling pathways, induction of neuronal death, and eventually, neuronal degeneration [143]. Glycation mediated by AGE formation in the brain has also been demonstrated at the periphery of Lewy bodies in PD patients [144]. The presence of AGEs in PD patients provides evidence that oxidative stress might be involved in the progression of PD [144], and accumulation of AGEs would mediate cellular stress, leading to neuronal death in PD [145].

Despite the important roles of RAGE in the pathogenesis of PD, further studies are warranted in order to understand the link between these receptors and the molecules involved in the development of this condition, as well as their importance in the lesion of the nigrostriatal pathway. Another key issue that deserves attention is the potential role of RAGE in non-motor symptoms of PD, which are very important comorbidities.

5.3. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease that affects the motor neuron, leading to muscle weakness, atrophy, paralysis, and consequently, death associated with respiratory failure [146-148].

Several studies have suggested that neuroinflammation [149, 150] and oxidative stress [151] might be involved in the progression of ALS. Since RAGE plays an important function in inflammation [65] and oxidative stress [152, 153], its correlation with ALS pathophysiology is likely to occur, being an important topic of investigation.

In ALS rodent models, such as mice carrying a mutation in superoxide dismutase 1 (SOD1), an increase of RAGE and its ligands in the spinal cord was demonstrated [154-157]. Daily administration of the recombinant sRAGE in SOD1 G93A mice retarded the onset of impaired motor function and reduced astrogliosis [154]. Moreover, primary astrocytes from mouse pup cortices of mutant SOD1 G93A mice have increased S100B expression in comparison to the control group. Silencing S100 in these cells reduced the production of proinflammatory mediators [156].

Glycation, an important process involved in the formation of AGEs, was observed in the central nervous system (CNS) of patients with ALS [107]. An immunoreactivity of AGEs with neurofilament conglomerates has been demonstrated. Authors suggested that the AGE formation leads to neurofilament damage, causing cellular aggregation and cell death [158]. Furthermore, increased levels of some AGEs were observed in the spinal cord of patients carrying mutations in SOD1 [157].

In addition to AGEs, the expression of RAGE, as well as the levels of other ligands, such as S100 and HMGB1, are increased in spinal cord tissues of ALS patients in comparison to age-matched individuals [74, 159-161]. Indeed, there is evidence suggesting that HMGB1 may be involved in the progression of ALS [162, 163]. In contrast to the results obtained from CNS samples, the levels of sRAGE were found to be reduced in the serum of ALS patients in comparison to the control group [164].

Interestingly, similar mechanisms mediated by RAGE activation, such as intracellular pathways associated with inflammation, oxidative stress and neuroinflammation, are observed in AD, PD and ALS. These common roles may suggest RAGE inhibitors as a general class that could be effective in the treatment of neurodegenerative diseases.

6. RAGE-BASED PHARMACOTHERAPY AND DRUG DEVELOPMENT

Since the pathophysiology of the previously described neurodegenerative diseases might be strictly linked to AGEs-RAGE, as well as to similar binding events and subsequent effects, this field clearly poses a promising area to explore tools aiming at the pharmacotherapy of these conditions.

A review paper [165] summarized important findings on the effects of the specific AGE inhibitor, aminoguanidine (pimagedine), and the AGE crosslink breaker, alagebrium, on the glycation pathway inhibition. Although a small therapeutic relevance for both compounds was found for the treatment of diabetic nephropathy in Type II Diabetes Mellitus patients, the results were somewhat inconclusive due to concerns regarding the safety and efficacy of these compounds, especially for aminoguanidine, which might hinder their use in the clinic. Moreover, Bolton and colleagues found that some patients developed glomerulonephritis and other side effects when twice-daily treated with 300 mg of pimagedine [166]. It is important to highlight that serum AGEs usually show decline in association with improvements in blood glucose levels regardless of the nature of the drug that was chosen for the treatment [167]. Therefore, overall glycemic profile control is still crucial to prevent complications associated with AGE accumulation.

Different classes of drugs are supposed to prevent AGE and AGE-precursor formation, including the arginine analogs, such as aminoguanidine, as well as alagebrium and pyridoxamine [168]. A variety of pre-clinical studies have demonstrated the effectiveness of AGE inhibitors, such as

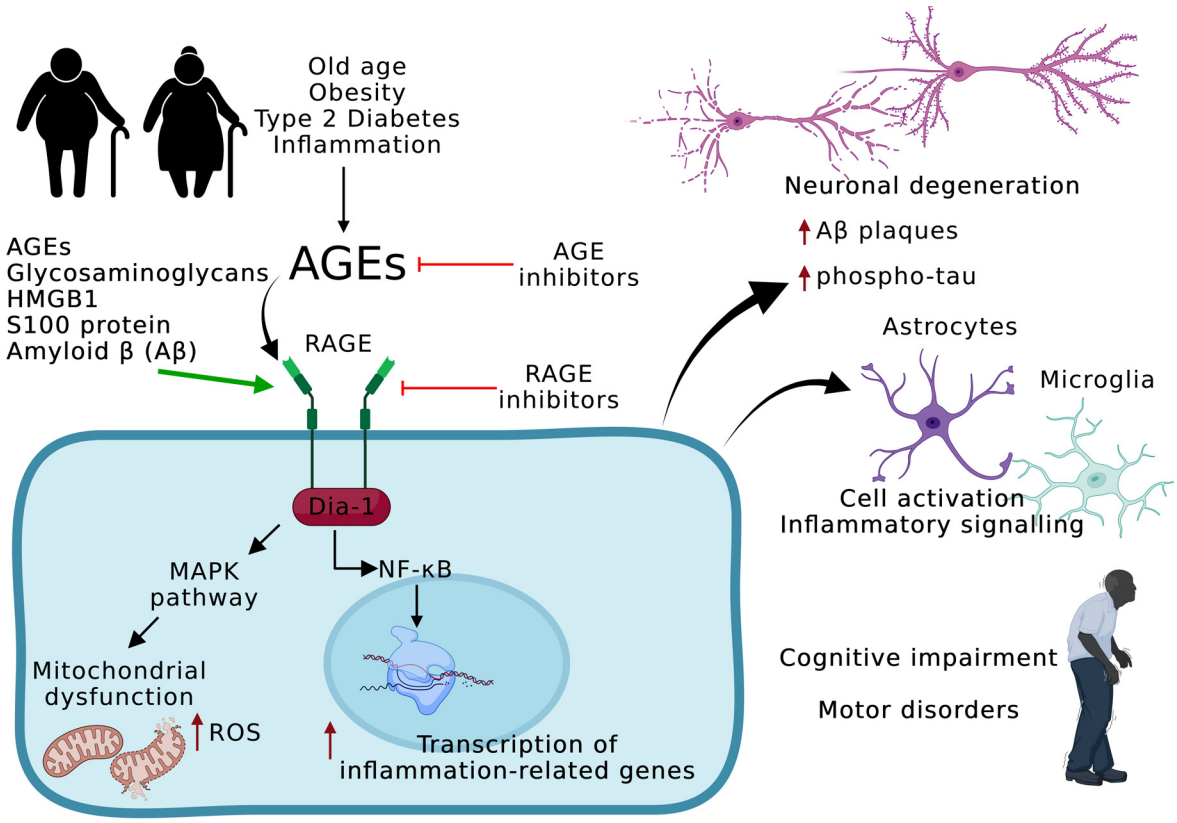

Fig. (5). Involvement of RAGE activation in neurodegenerative processes. Activation of RAGE in microglia, astrocytes or neurons could lead to the activation of signaling pathways associated with inflammation, oxidative stress, and cell death. Altogether, these events would contribute to the pathogenesis or aggravation of cognitive and motor disorders. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

alagebrium, in ameliorating the symptoms of diabetic nephropathy, neuropathy, retinopathy, and other complications related to AGE accumulation [169].

In this scenario, Sabbagh and coworkers evaluated the effects of PF-04494700 (azeliragon), an oral inhibitor of RAGE, in patients with mild-to-moderate dementia of the Alzheimer's type (Fig. **5**, Table **1**) Significant alterations in plasma levels of β -amyloid, inflammatory biomarkers, or secondary cognitive outcomes were found. The study concluded that a ten-week treatment protocol might be safe and well tolerated in patients with moderate-to-severe AD, and suggested a feasible protocol for long-term treatment with this drug [170]. Moreover, a recent study on the same compound showed that high doses of PF-04494700 were not well tolerated by the patients and produced symptoms of confusion, falls, and greater decline as assessed by the Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) [171]. However, low doses of 5 mg daily presented an appropriate safety profile and might be used in long-term treatment. PF-04494700 exerts its effects mainly in the extracellular compartment by preventing CML, Aβ42, S100B, and HMGB-1 binding to RAGE, and it can cross the blood-brain barrier [46].

The development of new AGE inhibitors could open an avenue for the treatment or prevention of different disorders, including neurodegenerative diseases. In this context, special attention is being given to the optimization of drug candidates, such as alagebrium or compounds structurally related to heterocyclic Schiff bases, in an attempt to overcome the drawbacks of the existing compounds, such as aminoguanidine, dimethylbisguanidine, N-Phenylacyl-1,3-thiazolium bromide (PTB), and N-Phenylacyl-4,5-dimethyl-1,3-thiazolium chloride (ALT-711) [172, 173].

Rational drug design is an important approach aiming at the development of new pharmaceutical tools for different diseases. In parallel, targeting risk factors by lowering the consumption of simple sugars is still a crucial strategy to reduce AGEs formation [174], since excessive carbohydrate intake is still one of the main driving factors towards AGE formation based on non-enzymatic alterations in protein structures as well as DNA post-translational changes [167]. In the context of glycemia control, antidiabetic drugs, such as metformin and others, might represent interesting approaches for reducing AGE formation. Despite their use for the treatment of diabetes, these drugs might have a potential therapeutic value in delaying the onset of neurodegenerative diseases or preventing further complications associated with AGE accumulation in the CNS tissues. Interestingly, despite its lowering blood glucose levels and dicarbonyl scavenging effects, metformin is also known to reduce RAGE signaling through AMPK-dependent blockade of ROS formation in an *in vitro* model of renal tubular cell injury [175], being a promising candidate in a possible repurposing approach.

Table 1. Summary of the main drug therapies for AGE-related complications.

Drug	Pharmacological Mechanism	Effects	Refs.
Aminoguanidine (pimagedine)	Inhibition of diamine oxidase and nitric oxide synthase	Reduction of advanced glycation end products (AGEs) levels through interacting with 3-deoxyglucosone, glyoxal, methylglyoxal, and related dicarbonyls	[165]
Alagebrium (3-phenacyl-4,5-dimethylthiazolium chloride [ALT-711])	Breaks on cross-link bonds between AGEs and lipids, proteins, and DNA in cells	Removal of the AGEs by cleavage of the abnormal cross-linking bonds. The effect has been associated with the modulation of inflammatory and sclerotic signaling pathways	[172]
N-Phenylacyl-1,3-thiazolium bromide (PTB)	Breaks in cross-link bonds	Prevention of vascular AGE accumulation	[173, 176]
Pyridoxamine	Trapping of intermediates in the formation of Amadori products released from glycated proteins	Prevention of AGE and AGE precursor formation	[168]
PF-04494700 (azeliragon)	Inhibition of RAGE - oral administration	Reduction in downstream RAGE signaling cascades	[170]
Metformin	Activation of AMP-activated protein kinase (AMPK) and reduction in RAGE signaling	Direct: dicarbonyl scavenging effect; Indirect: reduction in AGE formation through reductions in blood glucose	[167, 174, 177]

CONCLUSION

The pathophysiological relevance of AGEs due to their strict link to the daily intake of carbohydrates and the neurodegenerative process of CNS disorders highlights their relevance in the development of potential treatments to overcome worldwide health issues. Thus, the validation of RAGEs and related biochemical pathways as biological targets aiming at the development of inhibitors or equivalent pharmacotherapeutic tools might become a priority of current and future drug discovery efforts. In this context, the improvement in the knowledge on structural, physiological and pharmacological features of the targets and pathways, as well as the funding of endeavors aiming at short-term results, such as the search of drug candidates by repurposing approaches, must be continuously encouraged. The consistent possibility to achieve safe and effective treatments for challenging diseases, such as AD, PD and ALS, based on the AGEs-RAGE field is a fair reason to support it.

LIST OF ABBREVIATIONS

AD = Alzheimer's Disease
AGEs = Advanced Glycation End Products
APP = Amyloid Precursor Protein
BBB = Blood-Brain Barrier
CNS = Central Nervous System
COX-2 = Cyclo-Oxygenase 2
GSK = Glycogen Synthase Kinase
MAPK = Mitogen-Activated Protein Kinase
NOS = Nitric Oxide Synthase
PD = Parkinson's Disease
ROS = Reactive Oxygen Species
SVZ = Subventricular Zone
Tg = Transgenic Mice

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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