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Review

Advanced glycation endproducts and their receptor RAGE in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most common dementing disorder of late life. Although there might be various different triggering events in the early stages of the disease, they seem to converge on a few characteristic final pathways in the late stages, characterized by inflammation and neurodegeneration. In this review, we revisit the hypothesis that advanced glycation endproducts (AGEs) and their receptor RAGE may play an important role in disease pathogenesis. Accumulation of AGEs in cells and tissues is a normal feature of aging, but is accelerated in AD. In AD, AGEs can be detected in pathological deposits such as amyloid plaques and neurofibrillary tangles. AGEs explain many of the neuropathological and biochemical features of AD such as extensive protein crosslinking, glial induction of oxidative stress and neuronal cell death. Oxidative stress and AGEs initiate a positive feedback loop, where normal age-related changes develop into a pathophysiological cascade. RAGE and its decoy receptor soluble RAGE, may contribute to or protect against AD pathogenesis by influencing transport of β-amyloid into the brain or by manipulating inflammatory mechanisms. Targeted pharmacological interventions using AGE-inhibitors, RAGE-antagonists, RAGE-antibodies, soluble RAGE or RAGE signalling inhibitors such as membrane-permeable antioxidants may be promising therapeutic strategies to slow down the progression of AD.

Keywords: Advanced glycation endproducts; Nitric oxide; Alzheimer's disease; Inflammation; β-Amyloid; Glycation; Diabetes; Oxidative stress; RAGE; Soluble RAGE

1. Alzheimer's disease—epidemiology, histopathology and biochemistry

Alzheimer's disease (AD) is the most common cause of dementia. The prevalence of AD doubles every 5 years after the age of 60, with estimates being over 20% in those over 80 years (Yan et al., 1994). Developing pharmacological strategies to improve the quality of life for patients and to minimize the burden on caregivers is therefore an important task for the community. One of the pathological features of AD is the presence of high densities of 'neuritic plaques' in the neuropil of the cerebral cortex and hippocampus. β-Amyloid (Aβ) peptide is one of the main components of neuritic plaques, and this 40–42 amino acid peptide is widely regarded as a major contributor to the neurodegeneration that occurs in AD brains (Behl et al., 1994; Toth et al., 2007). Strong evidence

Abbreviations: Aβ, β-amyloid peptide; AD, Alzheimer's disease; AGEs, advanced glycation endproducts; BACE1, β-secretase; BSA, bovine serum albumin; CAA, cerebral amyloid angiopathy; CML, carboxymethyl-lysine; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; MAP, microtubule associated protein; M-CSF, macrophage-colony stimulating factor; MRPs, Maillard reaction products; MOLD, methylglyoxal linked dimmer; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NFT, neurofibrillary tangles; PKC, protein kinase C; PHFs, paired helical filaments; RAGE, receptor for advanced glycation endproducts; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α.

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for the involvement of Aβ comes from studies of early onset AD, which is inherited in an autosomatic dominant fashion, and in many afflicted families is associated with mutations in the amyloid precursor protein or the secretases that cleave it (Haass et al., 1994; Lichtenthaler et al., 1997; Takeuchi and Yamagishi, 2008). Other characteristics of AD are the intracellular accumulation of neurofibrillary tangles in pyramidal neurons, a local inflammatory process around the amyloid plaques and diminished glucose uptake and utilization in the brain (Schmidt et al., 2005). A direct link between all these phenomena is not established yet, and the discussion continues on whether AD is rather a syndrome with multiple independent pathologies developing at the same time in the aging brain or a disease with a single cause. Ten years ago, it was proposed that the chemical process which may be responsible for both, the observed extensive protein crosslinking and inflammation in AD, is the excess level of free radicals and reactive carbonyl compounds, leading to the formation of advanced glycation endproducts (AGEs) or advanced lipoxidation endproducts (ALEs) (Münch et al., 1997a,b).

2. Chemistry of advanced glycation endproducts (AGEs)

Oxidative stress is defined as an imbalance of radical production and detoxification. DNA oxidation products, such as 8-oxoguanosine, or protein oxidation products, such as dityrosine, are markers of oxidative stress and accumulate during aging and diseases correlated with inflammation (Vitek et al., 1994). In analogy, AGEs (and ALEs) are markers of carbonyl stress, which accumulate due to an increased level of sugars and reactive dicarbonyl compounds such as glucose, fructose, deoxyglucose, glyoxal, methylglyoxal and triosephosphates (Brownlee, 1995; Thornalley, 2003). AGE formation can also commence when amino groups of proteins, particularly the N-terminal amino group and side chains of lysine and arginine react non-enzymatically with these reactive carbonyl compounds. This post-translational modification, termed 'non-enzymatic glycosylation', 'glycation' or 'Maillard reaction', leads via reversible Schiff-base adducts to protein bound Amadori products. Through subsequent oxidations and dehydrations, including free radical intermediates, a broad range of heterogeneous fluorescent and yellow-brown products with nitrogen- and oxygen-containing heterocycles are formed, the so-called AGEs (Fig. 1). These latter reactions are accelerated by transition metals, such as copper and iron, which oxidize the protein-bound Amadori products or the monosaccharides directly in solution (Cochrane and Furth, 1993; Loske et al., 1998). Among physiologically relevant sugars, glucose is the least reactive, presumably the reason for its selection by evolution as the main biological energy carrier; the rank order of reactivity for the

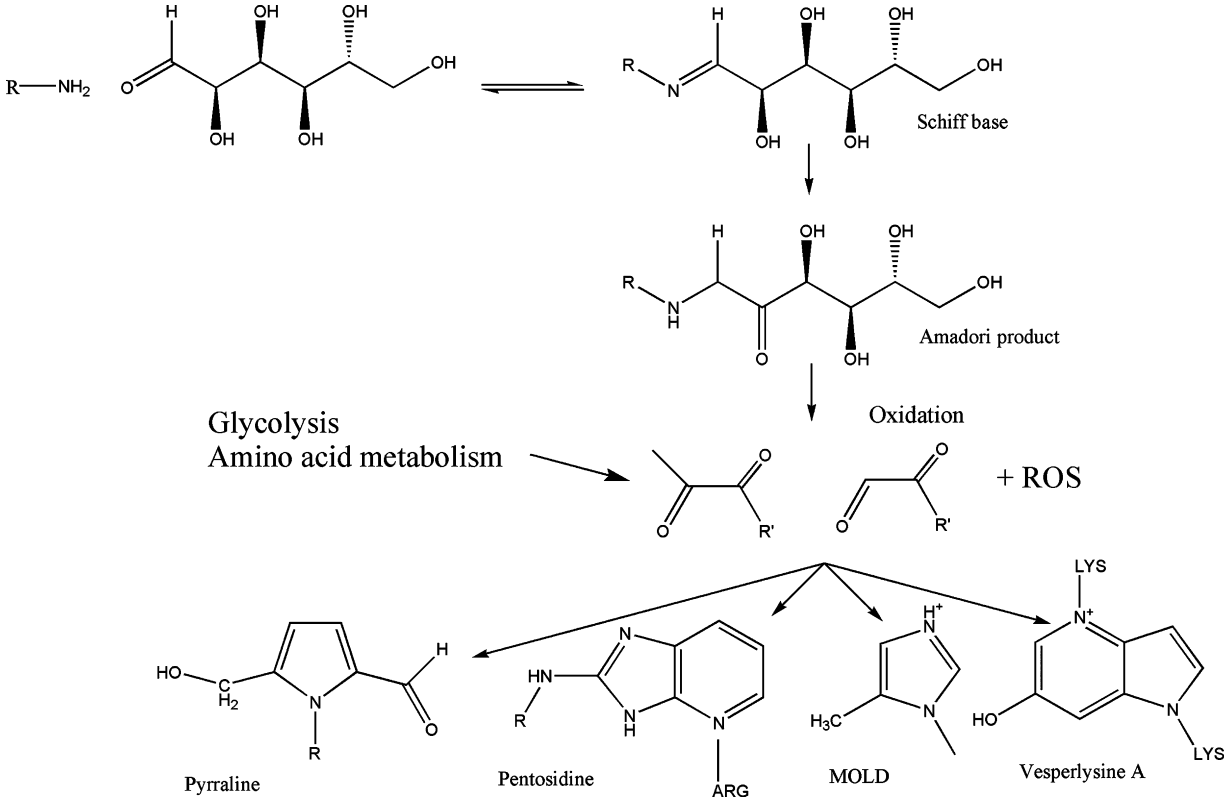

Fig. 1. Formation of advanced glycation endproducts on proteins. Arginine and lysine residues of proteins react with reducing sugars to form the Schiff base, which is rearranged to an Amadori product and finally, after oxidations, dehydrations and other rearrangements leads – via dicarbonyl compounds such as methylglyoxal – to the formation of (often crosslinked) advanced glycation endproducts (adapted from Münch et al., 1997a,b).

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other monosaccharides increases from hexoses to trioses and dicarbonyl compounds by several orders of magnitude (Iwata et al., 2004). AGE formation is irreversible and causes protease-resistant crosslinking of peptides and proteins, leading to protein deposition and amyloidosis. Using a library of dipeptides on cellulose membranes (SPOT library), we have systematically assayed the relative reactivities of amino acid side chains and the N-terminal amino group with sugars and protein-AGEs. Glucose and fructose react preferentially with cysteine or tryptophan when both the alpha-amino group and the side chains are free. In peptides with blocked N-terminus and free side chains cysteine, lysine, histidine – and to a much lesser degree – arginine were preferred. Crosslinking of protein-AGEs to dipeptides with free side chains and blocked N-termini occurred preferentially to arginine and tryptophan (Münch et al., 1999).

3. Advanced glycation endproducts in aging and degenerative diseases

In the 1970s and 1980s, Monnier and Cerami, the pioneers of the 'non-enzymatic glycosylation theory of aging' proposed that the AGE-mediated crosslinking of long-lived proteins contributes to the age-related decline in the function of cells and tissues in normal aging (Monnier and Cerami, 1981). Recent progress in the understanding of this process has confirmed that AGEs play a significant role in the evolution of vascular complications with aging, especially in diabetes and renal failure (Jerums et al., 2003). AGEs have been detected in vascular walls, lipoproteins and lipid constituents, where they lead to macroangiopathy, microangiopathy and amyloidosis. In particular, diseases such as atherosclerosis, cataract and diabetic nephropathy, retinopathy and neuropathy are suggested to be either caused or promoted by AGEs (Gasser and Forbes, 2008). The involvement of AGEs in brain aging and – in an accelerated fashion – in AD was first proposed in the mid 1990s (Simard et al., 2006; Ueda et al., 1994; Yan et al., 1996a,b). Distribution of AGEs has since then been investigated in various compartments and regions in the human brain in a disease and age-related manner. The stability of proteins that constitute the long-lived intracellular (neurofibrillary tangles and Hirano Bodies) and extracellular protein deposits (senile plaques) suggests that they would be ideal substrates for glycation, a process that occurs over a long time, even at normal levels of glucose, ultimately resulting in the formation of AGEs.

3.1. Intracellular AGE deposits

In humans, AGEs are localized in pyramidal neurons, exhibiting a granular, perikaryonal distribution. These pyramidal neurons appear to selectively accumulate AGE-containing vesicles in an age-dependent manner starting in the second decade of life (Sugaya et al., 1994). High resolution immunochemistry suggests that AGEs accumulate in endosomes or lysosomes, and that they appear to be a constituent of lipofuscin (Anzai et al., 2006; Horie et al., 1997). In the AD brain, extraneuroperikaryal AGE (carboxymethyllysine (CML) and pentosidine) deposits are co-localized with glial fibrillary acidic protein-positive astrocytes (Horie et al., 1997). We conducted a further study in which we compared the localization of AGEs and Aβ with inducible nitric oxide synthase (iNOS) in the auditory association area of the superior temporal gyrus (Brodmann area 22) of normal and AD brains. In aged normal individuals as well as early stage AD patients (i.e. no pathological findings in isocortical areas), a few astrocytes showed co-localization of AGE and iNOS in the upper neuronal layers, compared with no astrocytes detected in young controls. In late stage AD brains, there was a much denser accumulation of astrocytes co-localized with AGE and iNOS in the deeper and particularly upper neuronal layers. Also, numerous neurons with diffuse AGE- but not iNOS-reactivity, and few AGE- and iNOS-positive microglia were found (Wong et al., 2001). In a subsequent study, the age- and stage-dependent distribution of AGEs in neurons and glia in the same region (Brodmann area 22) of young and old non-demented controls were analyzed and compared with early and late stage AD. The percentage of AGE-positive neurons (and astroglia) increase both with age and, in AD patients, with the progression of the disease (Braak stages). Interestingly, nearly all of those neurons which show diffuse cytosolic AGE immunoreactivity also contain hyperphosphoryated Tau, suggesting a link between AGE accumulation and the formation of early neurofibrillary tangles (Lüth et al., 2005).

Neurofibrillary tangles (NFT) are further histological characteristics of AD (Braak and Braak, 1988). The progression rate of AD-related neurofibrillary changes is unknown, but initial changes occur 50 years before the disease is diagnosed. The major component of NFT, which consist of paired helical filaments (PHFs), is the microtubule associated protein (MAP)-Tau (for review, see Gotz, 2001). As early as 1994**,** AGEs were colocalized in NFTs by immunohistochemistry with specific AGE antibodies (Yan et al., 1996a,b). MAP-Tau is preferentially glycated at its Tubulin binding site, suggesting that glycation may be one of the modifications hampering the binding of Tau to Tubulin in AD, thus facilitating Tau aggregation into PHFs (Ledesma et al., 1994). Biochemical analysis of PHFs supports the immunohistochemical identification of AGEs in NFTs. With a CML antibody, the following human Tau preparations were probed: Tau of normal brains and preparations of soluble PHF-Tau as well as insoluble PHF from AD brains. All three principal Tau components resolved from PHF-Tau on Western blots showed CML immunoreactivity, indicating that Tau is glycated in PHF-Tau; insoluble PHF exhibited prominent CML immunoreactivity on top of the stacking gel. Moreover, immunoelectron microscopic analyses indicate that the anti-CML antibody labels predominantly PHF in aggregates (Ko et al., 1999). Taken together, these results suggest that Tau becomes glycated in PHF-Tau and that glycation may

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play a role in stabilizing PHF aggregation, leading to tangle formation in AD. The protein constituents of NFT are resistant to proteolytic removal, possibly as a result of extensive disulfide, dityrosine and AGE crosslinking, reinforcing the hypothesis that AD is a disease characterized by an imbalance of proteolytic regulation (Smith et al., 1995). The involvement of AGEs in this intracellular proteolytic dysregulation is supported by data, showing that crosslinked protein-AGEs have an inhibitory effect on the proteasome (Sternberg et al., 2008).

3.2. Extracellular AGE deposits

Increased extracellular AGE formation has been demonstrated in amyloid plaques in different cortical areas. In another immunohistochemical study, vascular walls in amyloid angiopathy were not labelled by a monoclonal AGE-antibody, while primitive plaques, coronas of classic plaques and some glial cells in affected regions of the AD brain were positive for AGEs (Kimura et al., 1995). In most senile plaques (including diffuse plaques) and cerebral amyloid angiopathy (CAA) from Alzheimer's brains, AGEs were observed. However, approximately 5% of these plaques were AGE positive but Aβ negative, and the vessels without CAA often showed AGE immunoreactivity (Salkovic-Petrisic and Hoyer, 2007). In AD, CML was found to be coexpressed with Tau protein, showing the similar neurofibrillary tangle shape as in neuritic plaques, but not in the core of amyloid plaques (Girones et al., 2004). These findings suggest that AGE formation may occur in the early stages of plaque formation in AD, but that AGE-epitopes disappear when the plaque ages or undergoes processing by microglia in the amyloid core.

There are only a few studies published so far, showing that AGE formation actively accelerates the conversion of Aβ from monomeric to oligomeric or high molecular weight forms. We and others could show that nucleation-dependent polymerization of Aβ peptide, the major component of plaques in patients with Alzheimer's disease, is significantly accelerated by crosslinking through AGEs (Loske et al., 2000). Our in vitro experiments using synthetic Aβ peptide and glucose or fructose show that formation of covalently crosslinked high molecular weight Aβ oligomers is accelerated by micromolar amounts of copper (Cu^{+}, Cu^{2+}) and iron (Fe^{2+}, Fe^{3+}) ions. This suggests that AGEs may indeed represent a driving force in the acceleration of Aβ deposition and plaque formation.

4. Direct toxic effects of advanced glycation endproducts

AGEs have been shown to be more than a harmless post-translational protein modification; various pathophysiological effects have been found at the cellular and molecular level. One of the proposed mechanisms of AGE-induced damage are reactive oxygen species (ROS), particularly superoxide and hydrogen peroxide released by AGEs (Carubelli et al., 1995; Muscat et al., 2007; Ortwerth et al., 1998). Formation of oxygen free radicals is associated with the oxidation of sugars and Amadori products. For example, protein glycation has been shown to increase the rate of free radical production at physiological pH nearly 50-fold compared with nonglycated protein (Mullarkey et al., 1990). This process commences with the production of superoxide radicals by transition metal-catalyzed autoxidation of the sugars and proteins bound Amadori products, followed by dismutation of superoxide to hydrogen peroxide and the generation of lethal hydroxyl radicals by the metal-catalyzed Fenton reaction. This can lead to a site-specific attack on the proteins with consequent protein damage and lipid peroxidation (Wolf et al., 2002). ROS production by food-derived Maillard reaction products (MRPs) is attracting considerable interest with regard to diseases, such as irritable bowel disease and – after resorption – diabetic complications including arteriosclerosis. For example, freshly brewed coffee and synthetic Maillard products produce >80 μM H_2O_2 and induce NF-κB translocation via the generation of hydrogen peroxide (Muscat et al., 2007).

Since the oxidation of glycated proteins, as shown above, as well as the interaction of AGEs with cell surface receptors, such as RAGE, produces superoxide radicals and hydrogen peroxide, it was suggested that AGEs could exert cytotoxic effects on cells. We have shown that two model AGEs, chicken egg albumin-AGE and bovine serum albumin (BSA)–AGE, both caused significant cell death in a dose-dependent manner (Loske et al., 1998). Cytotoxicity of the AGE-modified BSAs increased in correlation to the incubation time with glucose. Among the AGE-specific markers, browning (OD_{400nm}) correlated best with cytotoxicity, followed by AGE-specific fluorescence and the defined AGE, CML (Gasic-Milenkovic et al., 2001). Moreover, we wanted to measure if a similar effect can be observed with methylglyoxal-derived BSA–AGEs. The effect of different BSA–AGEs (derived from methylglyoxal) on cell viability, ROS formation, intracellular ATP levels, and activation of caspases 3/7 was tested in two human glial cell lines. All AGEs tested, regardless of their degree of modification, were found to induce ROS formation in both microglial (CHME-5) and astroglial cells (U373 MG), while only highly modified AGEs were able to decrease the cell viability and induce apoptosis (Bigl et al., 2008). In a further study, it was shown that differentiation, induced by retinoic acid, made cells more susceptible to AGE toxicity through anion superoxide and peroxide generation. Retinoic acid induced a marked increase in the expression of the NADPH oxidase subunit p47phox catalytic activity of protein kinase C δ (Nitti et al., 2007).

The cytotoxic effects of AGEs can be attenuated by α-ketoglutarate and pyruvate, by antioxidants such as α-lipoic acid and N-acetylcysteine, and by aminoguanidine, an inhibitor of iNOS. This suggests that ROS as well as reactive nitrogen species (RNS) contribute to AGE mediated cytotoxicity (Loske et al., 1998). Furthermore, we have shown

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that AGEs (BSA–AGE and Aβ-AGE) persistently increase the ratio of oxidized to reduced glutathione in a dose- and time-dependent manner in SH-SY5Y neuroblastoma cells (Deuther-Conrad et al., 2001). The level of oxidized glutathione accounted to 10–14% and persisted for up to 24 h in the presence of added AGEs. In contrast, the unmodified Aβ peptides (1–40) and (25–35) had no significant effect on glutathione redox status. The AGE-induced increase in oxidized glutathione could be prevented by the radical scavengers N-acetylcysteine, α-lipoic acid and 17β-estradiol or by application of catalase, indicating that superoxide and hydrogen peroxide production precedes the AGE-mediated depletion of reduced glutathione (Deuther-Conrad et al., 2001). In addition, we have shown that AGEs and Aβ (both ligands for the receptor for advanced glycation endproducts (RAGE); for details see Section 8) decrease glucose consumption, ATP levels and mitochondrial activity measured by MTT assay (Kuhla et al., 2004). However, only AGEs decreased the number of cells and increased lactate production. Although AGEs and Aβ have been generally thought to cause similar disturbances in neuronal metabolism, their complex signalling pathways appear to be quite distinct, a fact which should stimulate a more detailed investigation in this field, e.g. for the purpose of a rational design of potential "neuroprotective" RAGE antagonists (de Arriba et al., 2003; Kuhla et al., 2004).

5. Activation of macrophages and microglia by AGEs and other RAGE ligands

5.1. Activation by AGEs

The activation of microglial RAGE by many of its ligands, including AGEs and Aβ, results in the release of proinflammatory mediators such as free radicals and cytokines (Schmidt et al., 1994; Berbaum et al., 2008). AGEs, for example can induce the expression of proinflammatory cytokines through nuclear factor KB (NF-KB) dependent pathways via its receptor RAGE (see also Section 8 of this review). We have shown that chicken egg albumin-AGE induced nitric oxide (NO), tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) production involves both RAGE and the transcription factor NF-κB (Dukic-Stefanovic et al., 2003a,b). We have also demonstrated that the combination of Aβ and AGEs synergistically enhances the expression of the proinflammatory cytokines TNF-α, IL-6 and Macrophage colony-stimulating factor (M-CSF) (Gasic-Milenkovic et al., 2003). More AGEs accumulate on long-lived protein deposits, e.g. those composed of β_2-microglobulin (in dialysis-related amyloidosis) or Aβ peptide in AD. Using a cytokine bead array, we have analyzed the BSA–AGE induced expression of selected cytokines/chemokines in two murine cell lines, RAW 264.7 macrophages and N-11 microglia. Our study showed that monocyte chemoattractant protein-1 (MCP-1) and TNF-α were both released in a time-dependent manner from both RAW 264.7 macrophages and N-11 microglia upon stimulation with BSA–AGE or lipopolysaccharide (LPS), which was used as a positive control. Interestingly, MCP-1 was also constitutively expressed by unstimulated cells, although at a lower levels. Much higher levels of IL-6 were secreted by RAW 264.7 macrophages than by N-11 microglia in response to both stimuli. IL-12p70, IFN-γ and the anti-inflammatory cytokine IL-10 were not induced by either LPS nor BSA–AGE. Our results indicate a very similar pattern of chemokine and cytokine expression induced by such different ligands as AGEs and LPS, indicating similar or convergent downstream signaling pathways (Berbaum et al., 2008).

5.2. Activation of proinflammatory signalling by Aβ

One of the most interesting experiments in terms of proinflammatory signalling has been performed with isolated microglia and astrocyte cultures from rapid (4 h) brain autopsies of AD patients. Lue and colleagues showed increases in the production of pro-IL-1b, IL-6, TNF-α, MCP-1, macrophage inflammatory peptide-1a (MIP-1a), IL-8, and macrophage colony-stimulating factor (M-CSF) after exposure to pre-aggregated Aβ (1–42). In a further publication, they showed that Aβ (1–42) also activated more "proinflammatory" genes, such as indoleamine 2,3-dioxygenase and kynureninase, which are involved in formation of the neurotoxin quinolinic acid, and S100A8, a potential proinflammatory chemokine. Increased M-CSF secretion was also demonstrated using a cell culture model of plaques whereby microglia were cultured in wells containing focal deposits of immobilized Aβ (1–42). In each case, the Aβ stimulated M-CSF secretion was significantly blocked by treatment with RAGE antibodies (Lue et al., 2001). If Aβ mediated microglial activation persists for an extensive period of time, the resulting proinflammatory state may result in the death of neurons and drive the disease process (Rogers et al., 2007).

There is also evidence for a number of positive feedback loops by which inflammation in AD increases proinflammatory signalling through upregulation of its components through autocrine loops. Inflammation can produce more AGEs (will be discussed in Section 6) and there is also evidence that Aβ production is upregulated by inflammation. For example, TNF-α directly stimulates β-secretase (BACE1) expression and therefore enhances β-processing of the amyloid precursor protein (APP) in astrocytes, leading to increased amyloid deposition (Xia et al., 1997). Furthermore, there is evidence that RAGE is up-regulated by its own ligands. For example, increased levels of RAGE mRNA were observed in human osteoblasts after AGE–BSA treatment (Franke et al., 2007). In a similar study in human microvascular endothelial cells and ECV304 cells, AGEs and TNF-α were shown to activate the RAGE gene through the transcription factors NF-κB and Sp-1, causing enhanced AGE–RAGE interactions, which would lead to an exacerbation of AGE–RAGE mediated damage (Tan et al., 1998). Finally, incubation of microglia with M-CSF and Aβ increased expression of RAGE mRNA in microglia isolated from

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AD brains. These microglia also expressed M-CSF receptor mRNA. Overall, these studies suggest a positive feedback loop in which Aβ-RAGE-mediated microglial activation enhances expression of M-CSF and RAGE, possibly initiating an ascending spiral of cellular activation (Lue et al., 2001).

6. Factors promoting AGE formation in Alzheimer's disease

AGE production is increased in hyperglycaemic states such as diabetes, as well as in renal failure and hemodialysis due to the inability of the dialysis cartridges to remove AGE-modified peptides (Gerdemann et al., 2000). However, many additional factors including the involvement of C-3 and C-2 sugars and fragmentation products, even oxidized ascorbate, as well as transition metals and oxidative stress contribute to AGE formation in different tissues. In analogy to diabetes, many of the factors mentioned above may explain the elevated level of AGEs and AGE crosslinked proteins in the brain tissue of AD patients. In detail, the following disease-specific changes of AD may contribute to this process: (a) an intracellular increase in particular AGE reactive carbonyl compounds such as methylglyoxal as a consequence of inhibition of mitochondrial respiration, resulting from disturbed glucose metabolism; (b) an increase in unchelated transition metals such as copper and iron loosely bound to amyloid plaques, causing an acceleration of the oxidation of glycated proteins and subsequent increase in highly reactive glycoxidation products; (c) depletion of the antiglycation substance pool, for example the histidine dipeptides including carnosine and anserine; (d) defective Aβ clearance which increases the half-life of these peptides therefore enhancing its effect on AGE formation.

The increase of methylglyoxal levels in AD patients could be a consequence of the inhibition of glucose flux downstream of triose phosphates, e.g. in the lower part of glycolysis, the citric acid cycle and the oxidation of generated reducing equivalents through mitochondrial respiration. One cause of this inhibition could be ROS, which indirectly inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Du Yan et al., 1997). Some data show that hyperglycemia-induced GAPDH inhibition is a consequence of poly(ADP-ribosyl)ation of GAPDH by poly(ADP-ribose) polymerase (PARP), which is activated by DNA strand breaks produced by mitochondrial superoxide overproduction (Du et al., 2003). In addition, S-(2-succinyl)cysteine formation is described as a novel mechanism of inactivation of GAPDH through oxidative stress. S-(2-succinyl)cysteine is a chemical modification of proteins formed by a Michael addition reaction between the Krebs cycle intermediate, fumarate, and thiol groups in proteins—a process known as succination of protein by fumarate (Blatnik et al., 2008).

Unchelated transition metals such as copper and iron have been observed loosely bound to amyloid plaques (Lovell et al., 1998). These elements do not only increase oxidation of sugars and Amadori products, but foster the aggregation of Aβ peptides, bringing the monomers in close proximity for AGE-induced crosslinking (Loske et al., 2000). It has been proposed that depletion of the antiglycation substance pool, e.g. the histidine dipeptides including carnosine and anserine, by lipid peroxidation products such as acrolein could also be a reason for increased AGE formation in AD (Carini et al., 2003; Hipkiss, 2007; Reddy et al., 2005). When free amino acid (FAA) and dipeptide (DP) concentrations in probable Alzheimer's disease (pAD) subjects were compared with control subjects using liquid chromatography and electrospray ionization tandem mass spectrometry, carnosine levels were found to be significantly lower in pAD (328.4 ± 91.31 nmol/dl) than in control plasma (654.23 ± 100.61 nmol/dl) (Fonteh et al., 2007).

Furthermore, AGEs could contribute to the inability of microglia to clear plaques by introducing crosslinks to Aβ and other plaque associated proteins which makes it difficult to take up and degrade Aβ by inhibiting lysosomal proteases such as cathepsin D (Miyata et al., 1997; Schubert, 2005). We previously discussed the neuroprotective effect of microglia because of their potential to clear Aβ. Microglia express receptors that promote the clearance and phagocytosis of Aβ, such as class A scavenger receptor (SRA) and CD36 (Alarcon et al., 2005; Cho et al., 2005; Yan et al., 1996a,b). In particular, invading macrophages from the periphery can restrict senile plaque formation by phagocytosis of Aβ (Shoda et al., 1997). The paradox is that microglia may ultimately contribute towards plaque formation due to their failure to clear Aβ efficiently. Investigators have shown that, compared with younger mice, microglia from older transgenic presenilin 1 (PS1)-APP mice showed reduced expression of the Aβ-binding scavenger receptors SRA, CD36 as well as RAGE and the Aβ degrading enzymes insulysin, neprilysin, and MMP9, compared with their littermate controls (Hickman et al., 2008). In parallel, these microglia had increased expression levels of IL-1 and TNF-α, suggesting an inverse correlation between cytokine production and Aβ clearance. These data indicate that, although early microglial recruitment promotes Aβ clearance and is neuroprotective in AD, as the disease progresses, proinflammatory cytokines are produced in response to Aβ deposition (with RAGE as the Aβ-binding receptor), which then downregulate genes involved in Aβ clearance and promote Aβ accumulation. Microglia may thus contribute to plaque formation, accumulation of AGEs on plaques over time, more intense crosslinking, inflammation and chronic neurodegeneration.

7. AGE formation—one of the links between diabetes and Alzheimer's disease?

The deleterious effects of diabetes mellitus on the retinal, renal, cardiovascular, and peripheral nervous systems are widely acknowledged. Both types 1 and 2 diabetes mellitus have been associated with reduced cognitive performance

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(Kodl and Seaquist, 2008). Large prospective studies such as the Rotterdam study have demonstrated that type 2 diabetes mellitus is strongly associated with the risk of AD (Ott et al., 1999). The exact pathophysiology of cognitive dysfunction and dementia in diabetes is not completely understood, but it is likely that hyperglycemia, vascular disease, hypoglycemia and insulin resistance may all play some role. Glycation as a biochemical link between diabetes mellitus and Alzheimer's disease was suggested about 10 years ago (Smith and Perry, 1994; Smith et al., 1996a,b).

The role of AGEs and RAGE in the development of neuronal complications of diabetes such as polyneuropathy and dementia has recently attracted considerable attention (Thorpe and Baynes, 1996). It was hypothesized, that cognitive dysfunction in vascular dementia may relate to microvascular diseases, resembling that in diabetes. Brain sections from 25 cases of the OPTIMA (Oxford Project to Investigate Memory and Ageing) cohort, with varying degrees of cerebrovascular pathology and cognitive dysfunction (but only minimal Alzheimer type pathology) were immunostained for CML, the most abundant AGE. It was thought that, among people with cerebrovascular disease, (1) those with dementia have higher levels of neuronal and vascular AGEs and (2) if cognitive dysfunction depends on neuronal and/or vascular AGE levels. The probability of cortical neurons staining positive for CML was shown to be higher in cases with worse cognition or a history of hypertension. Additionally, vascular CML staining related to cognitive impairment and a history of diabetes (Smith et al., 1996a,b).

Continuous hyperglycemia is a causative factor of diabetic vascular complications, and it enhances the generation of AGEs through non-enzymatic glycation, thereby being involved in the pathogenesis of AD as well. Moreover, there is a growing body of evidence showing that the interaction of AGEs with RAGE elicits ROS generation and vascular inflammation, and subsequently alters various gene expressions in numerous cell types, all of which could contribute to the pathological changes of diabetic vascular complications and AD (Takedo et al., 1996).

There are other putative pathways by which type 2 diabetes mellitus may contribute to cognitive dysfunction. "Insulin resistance" of the brain is another possible pathway which may be related to cognitive dysfunction. Patients with Alzheimer's disease and normal glucose tolerance have been shown to have a stronger insulin secretory response to an oral glucose load than controls, suggesting that they may have increased insulin resistance (Bucht et al., 1983; Fujisawa et al., 1991). Others have hypothesized that the desensitization of neuronal insulin receptors may play a role in AD on observations by others that patients with AD have elevated insulin levels in the cerebrospinal fluid under fasting conditions (Fujisawa et al., 1991; Hoyer, 1998, 2004; Saletu et al., 1989). Several insulin-driven mechanisms have been postulated for cognitive impairment, including altered neurotransmitter function, increased production of amyloid plaques and disruption of the hypothalamic-pituitary adrenal axis (Kodl and Seaquist, 2008).

8. RAGE in age-related and neurodegenerative diseases

8.1. Biology of RAGE

RAGE, the receptor for advanced glycation endproducts, is a transmembrane receptor of the immunoglobulin super family, which was first characterized in 1992 (Brett et al., 1993; Neeper et al., 1992). It received its name because it was isolated by affinity chromatography with immobilized AGEs. The length of the unprocessed precursor of human RAGE (Swissprot accession number Q15109) is 404 amino acids (aa) and its molecular weight (without glycosylation) is 42,803 Da.

8.2. RAGE isoforms

The human RAGE gene (also termed AGER) is located on chromosome 6 in the MHC class III region and is composed of a 5' flanking region that regulates its transcription, 11 exons interlaced by 10 introns and a short 3' UTR (Stolzing et al., 2006). The human RAGE protein is composed of a number of distinct protein domains: an extracellular region (aa 1–342) composed of a signal peptide (aa 1–22), followed by three Ig-like domains, including an Ig-like V-type domain, which contains, at least in part, a proposed ligand binding site (aa 23–116) and two Ig-like C2-type 1/2 domains (aa 124–221 and 227–317); a single transmembrane domain (aa 343–363), and a short cytoplasmic tail (aa 364–404).

A number of splice variants and resulting protein isoforms of RAGE have been described, including a secreted extracellular form and a N-truncated form, lacking the ligand binding site (Casselmann et al., 2004; Hudson et al., 2008; Sasaki et al., 1998; Yesavage et al., 2002). However, a lack of consistency in these studies remains in terms of what variants were detected, how they were detected, whether these splice variants are biologically relevant, as well as the different nomenclature assigned to the isoforms identified (e.g., secreted forms have been named sRAGE1/2/3, esRAGE or hRAGEsec. To address this question systemically and to create a consistent nomenclature, Hudson et al. have identified a vast range of splice forms of RAGE, classified them according to the Human Gene Nomenclature Committee (HGNC) and named them RAGE (for the full-length protein) and RAGE v_1 to RAGE v_13 (for all detected splice variants) (Hudson et al., 2003). In both lung and human primary aortic smooth muscle cells, the canonical human RAGE full-length isoform was the most prevalent variant and accounted for 80% and 70% of detected transcripts, respectively. Another transcript, N-truncated RAGE, which lacks the N-terminal V domain and therefore does not bind ligand molecules had previously been suggested as a

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physiologically relevant RAGE splice variant (Yesavage et al., 2002). However, in the study by Hudson et al., this isoform could not be detected as a mature protein, suggesting that it may be a nonsense mediated decay (NMD) candidate as predicted by the rule that a stop codon more than 50 nucleotides upstream of the final exon-exon splice junction targets the mRNA species for degradation (Muhlemann et al., 2008). One of the most interesting RAGE variants is RAGE_v1, which occurs due to inclusion of intron 9 and deletion of exon 10, produces a reading frameshift at aa number 332 and creates a unique C-terminus sequence (EGFDKVREAEDSPQHM). RAGE_v1 has been termed endogenous secretory RAGE (esRAGE) or soluble RAGE (sRAGE), and can be secreted as a "soluble" form from cells in contrast to the other predicted soluble forms (RAGE_v3, v7, and v9); the latter were clearly identified only in cell lysates. RAGE is also able to be cleaved by metalloproteinases from the membrane, therefore leading to a circulating variant similar to esRAGE (Raucci et al., 2008). This reaction simultaneously generates sRAGE and a membrane-anchored C-terminal RAGE fragment (RAGE-CTF). The amount of RAGE-CTF increases when RAGE-expressing cells are treated with a γ-secretase inhibitor, suggesting that RAGE-CTF is normally further processed by γ-secretase (Zeng et al., 2004). esRAGE and total sRAGE are able to bind their ligands but since they are not anchored in the membrane, they do not cause cellular activation. It is suggested that they act as decoy receptors, lowering the level of functional RAGE binding. It has to be noted that not all studies measuring "soluble RAGE" differentiate between these two different pools of soluble RAGE. Two commercial ELISAs are available to date, total sRAGE antigen (R&D Systems, Wiesbaden, Germany) and esRAGE (B-Bridge International, Sunnyvale, USA), which employ antibodies raised against a generic sRAGE sequence and a unique esRAGE, respectively.

8.3. Full length RAGE in normal and pathophysiological states

RAGE is thought to play a role in normal physiological processes such as early development as it is expressed in precise patterns particularly in the central nervous system during the early stages of life. RAGE is expressed pre-natally in the external germinal layer and post-natally in the plasma membranes of the granule neurons of the external and internal granule cell layers and in Purkinje cells in the developing mouse cerebellum (Chou et al., 2004). RAGE is also found in other brain regions such as entorhinal cortex, hippocampus and superior frontal gyrus in humans (Chen et al., 2007).

In addition, full length RAGE has been found to be upregulated in a variety of chronic inflammatory disorders such as rheumatoid arthritis, chronic kidney disease, arteriosclerosis and some cancers. Immunostaining of bovine tissues showed RAGE in the vasculature, endothelium, smooth muscle cells and in mononuclear cells in these tissues. RAGE antigen was also visualized in bovine cardiac myocytes as well as in cultures of neonatal rat cardiac myocytes and in neural tissue where motor neurons, peripheral nerves, and a population of cortical neurons were positive (Brett et al., 1993). RAGE was also detected on macrophages, T cells, and some B cells in synovial tissue, suggesting its role in the pathogenesis of inflammatory joint disease (Drinda et al., 2004).

There is ample evidence that RAGE itself is upregulated in AD. For example, RAGE expression in capillaries of AD brain is significantly increased compared to control cases. Moreover, significant negative correlations between the Aβ burden of amyloid plaques and RAGE-positive capillaries in AD brains have been described (Jeynes and Provias, 2008). Another study shows that although neuronal RAGE immunoreactivity was decreased in AD hippocampus, a strongly positive microvascular RAGE immunoreactivity could be observed (Donahue et al., 2006). This study examined the immunohistochemical localization of Aβ, AGE, and RAGE in neurons and astrocytes from patients with AD and diabetes mellitus (DM) (Girones et al., 2004). Aβ, AGE-, and RAGE-positive granules were identified in the perikaryon of hippocampal neurons (especially from CA3 and CA4) in all subjects. In AD, most astrocytes contained both AGE- and RAGE-positive granules. In DM patients and control cases, AGE- and RAGE-positive astrocytes were very rare (Girones et al., 2004). These findings support the hypothesis that glycated Aβ and RAGE are taken up into astrocytes and degraded through the lysosomal pathway. In a further study, RAGE expression was shown to be present on microglia and neurons of the hippocampus, entorhinal cortex, and superior frontal gyrus in AD and nondemented (ND) individuals, with obviously increased numbers of RAGE-immunoreactive microglia in AD (Lue et al., 2001). In summary, the combination of high concentrations of RAGE ligands and an autocrine upregulation of RAGE might lead to a vicious cycle of RAGE mediated inflammation driving neurodegeneration in AD (Schmidt et al., 1994).

8.4. Soluble RAGE in pathophysiological states and in Alzheimer's disease

The two secretory isoforms of RAGE (the splice variant esRAGE and sRAGE cleaved from full length RAGE) both lack the transmembrane domain and therefore circulate in plasma. By competing with cell-surface RAGE for ligand binding, sRAGE may contribute to the removal or neutralization of circulating ligands thus functioning as a decoy. The associations of sRAGE with disease states or inflammatory markers are of interest and may be variable. Clinical studies have recently shown that higher plasma levels of sRAGE are associated with a reduced risk of diseases related to chronic inflammation and oxidative stress.

Reduced levels of sRAGE were shown to increase the risk for coronary artery disease in non-diabetic men (Falcone et al., 2005), essential hypertension (Geroldi et al., 2005) or albuminuria in patients with type 2 diabetes (Humpert et al., 2007). This latter study compared sRAGE and esRAGE as

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markers of vascular complications in patients with type II DM and showed that sRAGE but not esRAGE (the splice variant RAGE_v1) was independently associated with albuminuria in these patients. This study also showed that neither sRAGE nor esRAGE were associated with markers of glucose control or macrovascular disease (Humpert et al., 2007). In another study, serum levels of sRAGE were shown to be positively associated with MCP-1 and TNF-α levels in type 2 diabetic patients (Nakamura et al., 2007). Other studies have shown that the severity of renal dysfunction in type 2 diabetic patients was inversely correlated with esRAGE (RAGE v_1) levels (Gohda et al., 2008).

sRAGE has also been evaluated as a possible biological marker for neurodegenerative and neuroinflammatory diseases. For example, low sRAGE plasma levels were associated with greater disease severity in multiple sclerosis and the rate of clinical relapse (Steele et al., 2007). Some studies have also determined plasma sRAGE levels in relation to dementia. Emanuele et al. measured plasma sRAGE levels in a cross-sectional study of 152 patients with a clinical diagnosis of AD, 91 with vascular dementia and 161 control subjects. They showed that sRAGE levels were significantly reduced in the plasma of AD patients compared with either vascular dementia patients or non-demented controls (Emanuele et al., 2005). Moreover, a reduced level of circulating sRAGE was measured in patients with mild cognitive impairment (MCI). The reduction of sRAGE in MCI, as well as the anticipation of the disease in patients with the lowest sRAGE levels (<225 pg/ml), suggest a role of RAGE ligands in the pathogenesis of the disease (Ghidoni et al., 2008). Interestingly, another study demonstrated elevated plasma levels of sRAGE in centenarians suggesting that high levels of sRAGE in plasma might be a predictive marker of extreme longevity in humans (Geroldi et al., 2006). Since nearly all RAGE ligands are mediators of inflammation, sRAGE might be viewed as an endogenous biological anti-inflammatory molecule. Moreover, high sRAGE levels might downregulate excess inflammation as present in many degenerative diseases of the elderly.

8.5. Functions of RAGE at the blood–brain barrier (BBB)

In addition to its function as an "inflammatory" receptor, RAGE has also been described as a transporter protein at the blood–brain barrier (BBB). The reaction of RAGE with Aβ (and possible other RAGE ligands) at the luminal membrane of the BBB has been suggested to mediate entry of circulating Aβ into the brain across the BBB in mice and rats, guinea pigs and nonhuman primates (Mackic et al., 2002; Martel et al., 1996), whereas low density lipoprotein receptor related protein (LRP) controls the efflux of Aβ from the brain (for review, see (Zhang et al., 2008). Furthermore, RAGE at the BBB regulates NFκB-dependent activation of endothelium with expression of proinflammatory cytokines and adhesion molecules; and secretion of endothelin-1, resulting in cerebral blood flow (CBF) reductions. These findings suggest that vascular RAGE is a target for inhibiting pathogenic consequences of Aβ-vascular interactions, including development of cerebral amyloidosis and inflammatory neurodegeneration (Deane et al., 2003). Compared with other small peptides, such as vasopressin or enkephalins (Zlokovic et al., 1985, 1989), RAGE-mediated transport of Aβ40 across the mouse BBB was two- to threefold faster, although it was only a fraction of the rate determined for amino acid transport, either across the BBB or the choroid plexus (Zlokovic et al., 1985; Zlokovic, 2008).

9. AGEs and RAGE as drug targets in Alzheimer's disease

Besides AGEs, RAGE is also able to bind other ligands and is thus often referred to as a "pattern recognition" receptor. RAGE binds S100 proteins, amphoterin (HMBG-1) as well as Aβ, which is the major protein component of plaques in AD (Bierhaus et al., 2005; Bucciarelli et al., 2002). Binding of any of these molecules is able to cause sustained cellular activation – often of proinflammatory signal cascades – as well as gene transcription (Clynes et al., 2007). For a detailed description of S100 and amphoterin and their cellular effects, the reader should consult the excellent reviews on S100 (Donato, 2001; Heizmann et al., 2007) and amphoterin/HMBG-1 (Lotze and Tracey, 2005; Rauvala and Rouhiainen, 2007). In AD brains, neuritic plaques contain both fibrillar Aβ and AGEs, which are both able to bind and activate RAGE signalling. Activation of RAGE by AGEs has been described in Section 5, and similar proinflammatory effects have been described for Aβ. For example, Aβ has been shown to induce the expression of neuronal and microglia M-CSF (Du Yan et al., 1997; Lue et al., 2001). Although it is not clear which of the two RAGE ligands in senile plaques is the most relevant one in terms of pathogenic principles in AD, the target RAGE is considered important, and therefore it is assumed that decoy receptors of RAGE, RAGE antagonists or RAGE antibodies would be able to attenuate neurotoxicity and/or inflammation mediated by both ligands, and slow down disease progression (Hudson et al., 2003; Yonekura et al., 2003).

9.1. AGE-inhibitors

An AGE-inhibitor is defined as a substance, which inhibits the covalent crosslinking of proteins and peptides by sugars or sugar derived oxidation products. It contains a nucleophilic amino group which competes with lysines in side chains of proteins for reactive carbonyl or dicarbonyl groups present on proteins and in solution (Rahbar et al., 2000a,b). Since the crucial step of AGE crosslinking depends on the presence of transition metals for the formation of glycoxidation products and radicals, metal chelators and radical scavengers, especially superoxide dismutase mimetics, could

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also be regarded as AGE-inhibitors in a broader sense of the definition (Price et al., 2001). Several natural and synthetic compounds have been shown to be inhibitors of AGE-formation in vitro and in vivo. Aminoguanidine was the first AGE-inhibitor, which was tested in vitro crosslinking experiments, then shown in various animal models to attenuate the AGE-mediated vascular complications of diabetes (Tanaka et al., 2000; Thomas et al., 2005). Tenilsetam, a cognition-enhancing and a purported anti-dementia drug (Pepeu and Spignoli, 1989), was also shown to be an effective AGE inhibitor and metal chelator (Price et al., 2001; Sebekova et al., 1998). Tenilsetam reacts with sugars and glycated proteins and acts as an inhibitor of AGE-induced amino acid and protein crosslinking in vitro (Braak and Braak, 1988). Tenilsetam, aminoguanidine and carnosine significantly inhibit nucleation-dependent polymerization of Aβ peptide with similar efficacy (Blatnik et al., 2008). The positive effects of AGE-inhibitors with respect to the reduction of Aβ toxicity may be attributable to formation of 'masked', less toxic and less crosslinked AGE peptide aggregates. The mechanisms by which AGE inhibitors could be beneficial in AD are quite diverse. AGE-inhibitors could shift the metabolic AGE balance in the direction of degradation and clearance rather than accumulation. AGE-inhibitors could also modify the structure of AGEs in a way which inhibits their binding to and recognition by AGE receptors including RAGE. These mechanisms might subsequently lead to a diminished inflammatory response and decreased oxidative stress. One (unpublished) double-blinded, randomized clinical trial with the AGE-inhibitor tenilsetam was conducted in 1989 with 75 AD patients. The drug significantly improved many clinical and psychometric scores including shortening of P300 latencies in the acoustic evoked potential, global clinical impression, Sandoz clinical assessment geriatric scale, Folstein minimental state scale and shopping list (Cassella AG, Frankfurt, Germany, unpublished observation).

9.2. RAGE antagonists, RAGE antibodies and soluble RAGE

It has been shown that RAGE ligands including Aβ and/or AGEs present in the AD brain elicit a significant inflammatory response in AD (Bucciarelli et al., 2002). RAGE is therefore (and additionally due to its function as Aβ transporter into the brain) considered a key target in the inflammatory and neurotoxic cascade which contributes to the progression of AD. There is a link between production of proinflammatory signals and the activation of the transcription factor NF-κB by RAGE in microglia. Intracellular signalling pathways such as those including mitogen activated protein kinase (MAPK) and protein kinase C (PKC) are able to cause the nuclear translocation of NF-κB and subsequent transcription of target genes (Fig. 2). The nuclear translocation inhibitor of NF-kB, SN50 and various MAPK inhibitors are able to significantly decrease production of many proinflammatory signals in response to RAGE ligands (Berbaum et al., 2008).

9.2.1. RAGE antibodies

In vitro assays have demonstrated that RAGE antibodies that block the binding of ligands to RAGE significantly decrease cytokine and nitric oxide production by microglia (Berbaum et al., 2008). In vivo studies have also supported

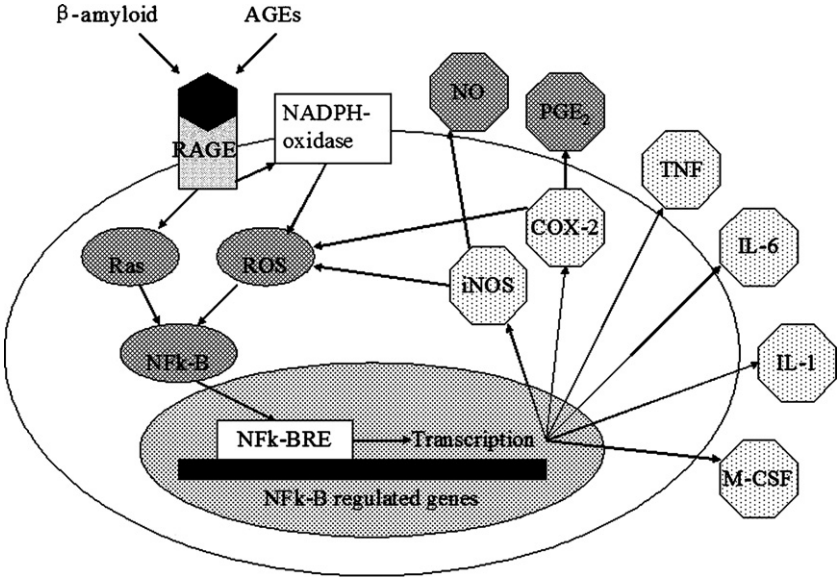

Fig. 2. Proinflammatory NF-κB signalling through RAGE. Activation of the receptor for advanced glycation endproducts activates the transcription factor NFκ-B via Ras and redox-sensitive signaling pathways, leading to transcription of genes coding for inducible nitric oxide synthase and a variety of cytokines including IL-1, IL-6 and TNF-α.

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RAGE as a therapeutic target, since a decrease in cytokine production is displayed in mice when they are pretreated with an anti-RAGE antibody prior to exposure with ligands of RAGE (Blatnik et al., 2008).

9.2.2. RAGE—antagonists

It is believed that RAGE antagonists might be beneficial in the treatment of several RAGE-related conditions including AD. Although no preclinical data have been published about Transtech Pharma's drug TTP488 (now PF 04494700), a double-blind, placebo-controlled, randomized, multicenter study conducted under the Alzheimer's Disease Cooperative Study to evaluate the efficacy and safety for 18 months of treatment with PF-04494700 (TTP488/PF 04494700) in participants with mild-to-moderate Alzheimer's disease began with patient enrollment in December 2007 (Brownlee, 1995).

9.2.3. Soluble RAGE

By competing with cell-surface expressed RAGE for ligand binding, sRAGE may contribute to the removal or neutralization of circulating ligands thus functioning as a decoy. Studies have suggested that treatment of diabetic apolipoproteinE (apoE)-null mice with sRAGE suppressed early acceleration of arteriosclerosis (Anzai et al., 2006). In particular, lesion formation, parameters of inflammation as well as mononuclear phagocyte and smooth muscle cell activation were decreased (Anzai et al., 2006). In another study, sRAGE showed beneficial effects in late stages of diabetes in the NOD mouse-disease transferred with diabetogenic T cells and recurrent disease in NOD/scid recipients of syngeneic islet transplants. Treatment of recipient NOD/scid mice with soluble RAGE prevented transfer of diabetes and delayed recurrent disease in syngeneic islet transplants. The authors concluded that RAGE/ligand interactions are involved in the differentiation of T cells to a mature pathogenic phenotype during the late stages of the development of diabetes, and that this could be prevented by application of sRAGE (Anzai et al., 2006). Hepatic ischemia/reperfusion (I/R) injury associated with liver transplantation and hepatic resection is characterized by hepatocellular damage and a deleterious inflammatory response. Animals treated with sRAGE, displayed increased survival after total hepatic I/R compared with vehicle treatment, and the authors suggest that the blockade of this pathway by sRAGE may represent a novel strategy to attenuate injury in hepatic I/R and to facilitate regeneration (Blatnik et al., 2008).

9.3. Membrane permeable, anti-inflammatory antioxidants

Antioxidants are able to scavenge both extracellular and, depending on their membrane-permeability, intracellular ROS, before these are able to damage cellular constituents or act as secondary messengers in inflammation. One of the primary redox-sensitive transcription factors in the RAGE pathway activated by ROS is NF-κB (Alarcon et al., 2005). NF-κB is not only capable of inducing cytokines, but can also increase expression of iNOS, through the NF-κB binding elements contained in the iNOS promoter sequence (Behl et al., 1994). The product of iNOS, NO, is involved in many cellular functions and may become more cytotoxic after conversion to the powerful oxidant peroxynitrite. Several of the steps in the AD inflammatory pathway involve the production of radicals, such as superoxide and nitric oxide, which are both products of microglia and astrocytes via RAGE stimulation by Aβ or AGEs (Alarcon et al., 2005). We have shown that membrane permeable antioxidants including α-lipoic acid can attenuate inflammatory pathways, such as AGE-induced iNOS expression (Berbaum et al., 2008). Although many epidemiological studies suggest that there is a connection between antioxidants and a reduced risk of AD, only a few trials with single antioxidants including Vitamin E, estrogen, and α-lipoic acid have displayed some benefits for AD patients, suggesting that these drugs are only effective in very early stages of the disease. However, there is evidence that a combination of antioxidants as part of a healthy nutrition is more effective than single, often synthetic antioxidants (Alarcon et al., 2005; Behl et al., 1994).

10. Conclusion

Many of the degenerative changes described in AD, such as increased oxidative stress and formation of AGEs resemble processes seen in other diseases including late complications in diabetes and long-term hemodialysis. The 'glycation theory of aging', as the underlying common principle of degeneration, unites some of the neuropathological and biochemical findings in AD to a general picture (Alarcon et al., 2005). AGEs may contribute to several processes underlying dementia including the accelerated protein crosslinking with β-amyloid and MAP-Tau. In addition, AGEs and other RAGE ligands including Aβ can lead to increased inflammation, oxidative stress and subsequent neuronal dysfunction. Pharmacological intervention using antioxidants, RAGE antagonists, antibodies and soluble RAGE and AGE-inhibitors may be a promising combined approach for minimizing AGE formation in aging and degeneration in general, and especially the resulting pathological effects in Alzheimer's disease.

Conflict of interest

There are no actual or potential conflicts of interest.

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