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Toxic Advanced Glycation End Products (TAGE) Theory in Alzheimer's Disease

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Several epidemiological studies have reported moderately increased risks of Alzheimer's disease (AD) in diabetic patients compared with general population. In diabetes mellitus, the formation and accumulation of advanced glycation end products (AGEs) progress more rapidly. Recent understanding of this process has confirmed that interactions between AGEs and their receptor (RAGE) may play a role in the pathogenesis of diabetic complications and AD. The authors have recently found that glyceraldehyde-derived AGEs (AGE-2), which is predominantly the structure of toxic AGEs (TAGE), show significant toxicity on cortical neuronal cells and that the neurotoxic effect of diabetic serum is completely blocked by neutralizing antibody against the AGE-2 epitope. Moreover, in human AD brains, AGE-2 is distributed in the cytosol of neurons in the hippocampus and parahippocampal gyrus. These results suggest that TAGE is involved in the pathogenesis of AD as well as other age-related diseases. In this review, the authors discuss the molecular mechanisms of AD, especially focusing on TAGE-RAGE system.

Keywords: advanced glycation end product (AGEs); glyceraldehyde-derived AGEs (AGE-2); toxic AGE (TAGE); receptor for AGEs (RAGE); Alzheimer's disease (AD); diabetic complications

Alzheimer's disease (AD) is characterized pathologically by the presence of senile plaques and neurofibrillary tangles (NFTs) at extracellular and intracellular sites, respectively. Senile plaques consist of the amyloid β (Aβ) protein, and its deposition is considered to be an early and causative event in the pathogenesis of AD, increasing markedly during the progression of the disease and leading in turn to the generation of NFTs and finally to neuronal death.[1] NFTs are composed of paired helical filaments (PHFs) and straight filaments. The major component of PHFs is the microtuble-associated protein τ.[2-4] In PHFs, τ shows distinctive properties, such as high aggregation, hyperphosphorylation, and other posttranslational modifications, including glycosylation, ubiquitination, glycation (formation of advanced glycation end products [AGEs]), polyamination, nitration, and proteolysis.

There have been variable reports on whether type 2 diabetes mellitus (DM) is a clinical risk factor for AD. Recent evidence from population-based studies does indicate a link between DM and AD, with an incidence of AD as much as 2 to 5 times higher in diabetic patients.[5-8] In addition to AD, other neurodegenerative diseases, such as Huntington's disease, Friedrich's ataxia, Werner's disease, and myotonic dystrophy, are associated with the development of DM.[9-12] Continuous hyperglycemia is a causative factor for diabetic complications, and it enhances the production of AGEs through the Maillard reaction. AGEs were originally

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characterized by a yellow-brown fluorescent color and an ability to form cross-links with and between amino groups,[13] but the term is now used for a broad range of advanced products of the Maillard reaction,[14-16] including N-carboxymethyllysine (CML) and pyrroline, which show neither color nor fluorescence and do not cross-link proteins.[17,18] CML can be formed from the precursors glyoxal and glycolaldehyde by an intramolecular Cannizzaro reaction, a process that is largely independent of glucose autoxidation.[19]

The formation and accumulation of AGEs in various tissues are known to progress during normal aging and at an accelerated rate in DM.[20-22] Recent understanding of this process has confirmed that AGEs interaction with their receptors (RAGE) play a role in the pathogenesis of diabetic complications and neurodegenerative disorders, including AD.[20-22] The aggregation of Aβ is promoted by its glycation in vitro.[23] Moreover, the glycation of τ, in addition to hyperphosphorylation, appears to enhance the formation of PHFs.[24,25] AGEs are likely important factors in the progression of neurodegenerative disorders that are characterized by protein aggregation and deposition. Recently, we showed that glyceraldehyde-derived AGEs (AGE-2) and glycolaldehyde-derived AGEs (AGE-3), but not glucose-derived AGEs (AGE-1) or CML, contribute to neuronal cell toxicity in diabetic patients, and it was emphasized that both contributing types of AGEs have high toxicity. We proposed that 2 groups of AGEs are associated with the cell toxicity: toxic AGEs (TAGE)[26-30] and nontoxic counterparts such as CML, pentosidine, pyrraline, and crossline. This review summarizes the molecular mechanisms of AD, focusing on the TAGE-RAGE system.

Formation of AGEs In Vivo

AGEs form by the Maillard reaction, a nonenzymatic reaction between ketones or aldehydes and the amino groups of proteins, which contributes to the aging of proteins and to the pathological complications of diabetes.[31-35] In DM, reducing sugars including glucose, fructose, and trioses (such as glyceraldehyde) are known to react with the amino groups of proteins nonenzymatically to form reversible Schiff bases and then Amadori products. These early glycation products undergo further complex reactions such as rearrangement, dehydration, and condensation to become irreversibly cross-linked, heterogeneous fluorescent derivatives termed *AGEs*.[36,37] Recent studies have suggested that AGEs can arise not only from sugars but also from carbonyl compounds derived from the autoxidation of sugars and other metabolic pathways.[19,38-40] In a previous report,[41-44] we described the contribution of glucose, α-hydroxyaldehydes (glyceraldehyde and glycolaldehyde), and dicarbonyl compounds (methylglyoxal [MGO], glyoxal [GO], and 3-deoxyglucosone) to the glycation of proteins, and we developed anti-AGEs antibodies that specifically recognize 6 distinct classes of AGEs structures (AGE-1; AGE-2; AGE-3; AGE-4, MGO-derived AGEs; AGE-5, GO-derived AGEs; and AGE-6, 3-deoxyglucosone-derived AGEs), but not CML structure, within the circulating proteins and peptides present in serum from type 2 diabetes patients undergoing hemodialysis. These results suggest that all 6 forms of AGEs were synthesized in vivo. Based on these data, we proposed a pathway for the formation of distinct AGEs by the Maillard reaction, sugar autoxidation, and sugar metabolic pathways in vivo, as shown in Figure 1.

Moreover, AGE-1 and AGE-2 are present in human serum, and the level of both of these AGEs is elevated in type 1 and type 2 diabetic patients.[45-47] These AGEs, especially the AGE-2-epitope, elicit angiogenesis at the concentrations present in the plasma of diabetic patients. The results therefore suggest the relevance of the AGE-2 epitope in the pathologic angiogenesis in vivo. We demonstrated for the first time that vitreous levels of both AGE-2 and vascular endothelial growth factor (VEGF) were significantly higher in diabetic patients than in control subjects and that these levels were elevated in association with the severity of neovascularization in diabetic retinopathy.[48]

Receptor for AGEs

Receptors could play a critical role in AGEs-related biology and the pathology associated with diabetic complications and aging disorders.[49-52] Several AGEs-binding molecules have been described, and it is thought that many of the adverse effects caused by advanced glycation are mediated via AGEs receptors, such as RAGE,[53] oligosaccharyl transferase-48 (AGE-R1),[54] galectin-3 (AGE-R3),[55] CD36,[56] macrophage scavenger receptors types 1 and 2,[57] and FEELs-1 and -2 (fasciclin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptors 1 and 2).[58] The relative pathogenic contribution of these receptors in

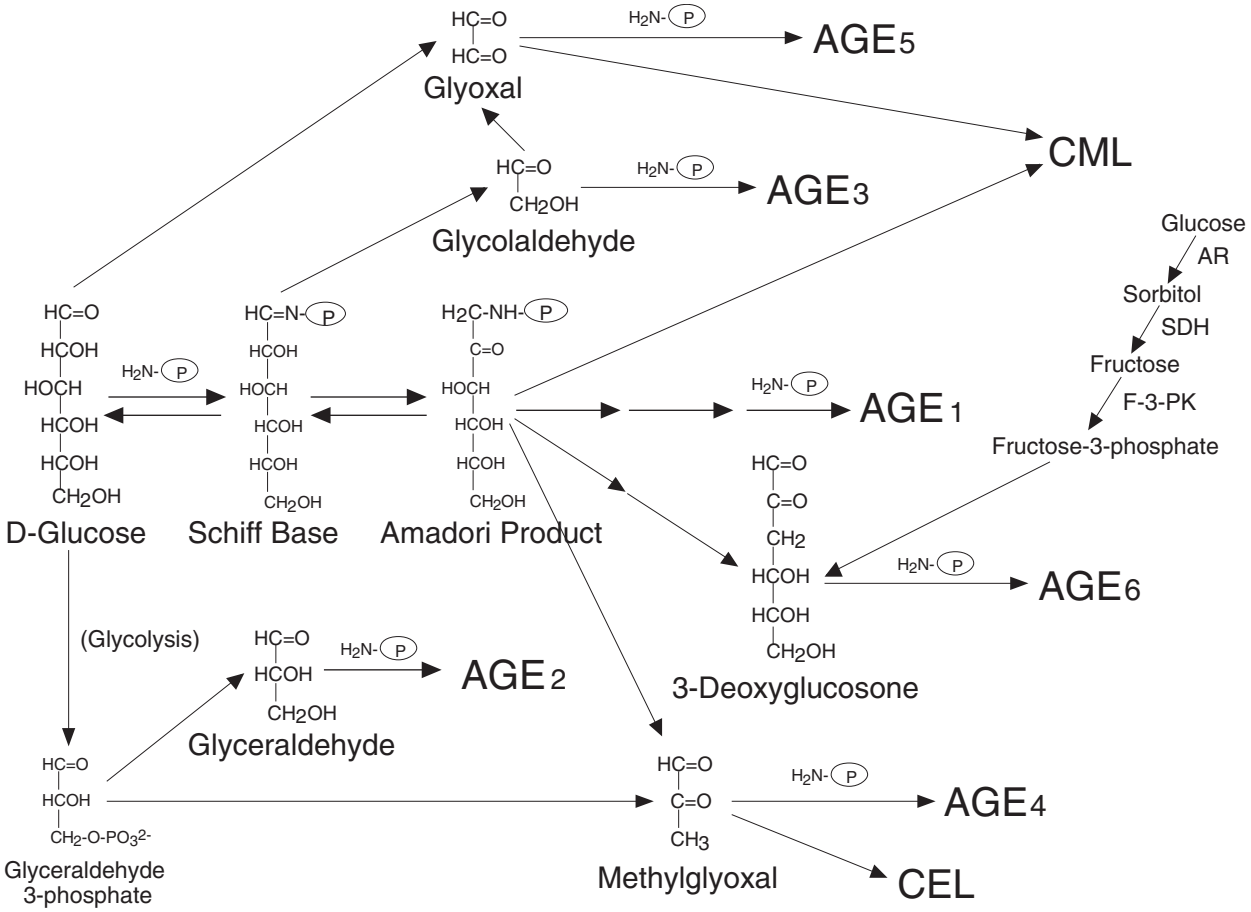

Figure 1. Synthesis of 6 distinct advanced glycation end products (AGEs) in vivo. CML = N-carboxymethyllysine; CEL = N-carboxyethyllysine; P-NH_2 = free amino residue of protein; AR = aldose reductase; SDH = sorbitol dehydrogenase; F-3-PK = fructose-3-phosphokinase.

diabetic complications is poorly defined, although RAGE is by far the best characterized mechanism during in vitro and in vivo studies on RAGE, and its regulatory fragments, such as soluble RAGE (sRAGE), indicate an important role in pathobiology.[52,59] BIAcore surface plasmon resonance assays demonstrated that AGE-2 and AGE-3 (K_d values for RAGE were estimated to be 0.3 μM and 1.4 μM, respectively), but not AGE-1, AGEs-4 to -6, CML, or pentosidine, were specifically bound to RAGE.[60,61]

RAGEs has also been proposed to play a major role in the onset of the AD. RAGE is expressed in a variety of cell types, including endothelial cells, pericytes, mesangial cells, neurons, and glia.[62-64] RAGE has been found to be a specific cell-surface receptor for Aβ peptide, thus eliciting neuronal cell perturbation.[62,65] The active participation of RAGE in the pathogenesis of AD has been confirmed in animal models; double transgenic mice with neuronal overexpression of neuronal RAGE and mutant amyloid precursor protein (mAPP) displayed early abnormalities in spatial learning/memory, accompanied by altered activation of markers of synaptic plasticity and exaggerated neuropathological findings, before such changes were found in mAPP transgenic mice.[66]

Relationship Between DM and AD

The relationship between DM, cognitive decline, and AD is still under active investigation, but some studies suggest that DM may be associated with an increased risk of developing AD, along with enhanced decline in some cognitive systems.[67,68] The Rotterdam Study, which surveyed more than 6300 patients, showed a relation between DM and AD, with a relative risk (RR) of 1.9.[5] Of particular note, given the recent interest in insulin dysfunction and AD,[69-72] patients in that study receiving exogenous insulin therapy were at the highest risk (RR = 4.3)

of dementia. The Honolulu-Asia Aging Study, which examined a cohort of 2574 patients, showed also that DM patients' risk was 1.8 for AD and 2.3 for vascular dementia.[7] Recently discovered links between DM and AD are indications of AGEs and increased RAGE expression in brains of patients with AD.[62,73] As AGEs are involved in diabetes complications, diabetes might influence AD brain pathology.

To what extent do circulating AGEs play a role in AD pathology? The degradation products of AGEs-modified proteins are not cleared during renal dialysis of diabetic patients.[41,74] These low-molecular-weight AGEs have been shown to be chemically reactive and to contribute to the further modification and damage of tissue proteins.[74] It remains of interest to determine whether AGEs formation is involved in abnormal τ-protein processing and in the deposition of Aβ that has been observed in the brains of patients undergoing renal dialysis.[75] Riviere et al quantified plasma protein glycation specifically derived from glucose in AD patients.[76] Protein glycation in plasma, evaluated by plasma furosine, was almost 2 times greater in subjects with AD than in controls but still 50% less than in subjects with DM. Recently, Shuvaev et al studied changes in the level of an early glycation product, an Amadori product, in cerebrospinal fluid (CSF) in aging patients and in those with late-onset AD.[77] The concentration of an Amadori product in CSF correlated with the CSF glucose concentration but did not change with age. In contrast, the level of CSF Amadori product was 1.7 times greater in AD patients than in a nondemented age-matched control group.

We have found that AGE-2 and AGE-3 cause apoptosis of retinal pericytes and induce VEGF after the interaction with RAGEs.[27,78,79] AGE-2 and AGE-3 also induce VEGF expression, DNA synthesis, and angiogenesis in microvascular endothelial cells (ECs), which are the hallmark of proliferative diabetic retinopathy. Although the molecular mechanisms of VEGF overexpression elicited by AGEs are not fully understood, our recent investigation has shown that the AGE-2–RAGE interaction might increase VEGF gene transcription in ECs by NADPH oxidase-mediated reactive oxygen species generation and the subsequent nuclear factor κB activation via Ras-mitogen-activated protein kinase pathway.[80,81] In mesangial cells, cell growth is inhibited by AGEs, especially by AGE-2 and AGE-3, with a strong inhibitory property. Furthermore, AGEs stimulate the secretion of VEGF and monocyte chemoattractant protein-1, where AGE-2 shows the strongest effects on the secretion.[28] Sekido et al[29] showed that cell viability and replication of Schwann cells as well as their production of proinflammatory cytokines, tumor necrosis factor–α, and interleukin-1β, were significantly affected by AGE-2 and AGE-3. Taken together, AGE-2 participates in the development of diabetic complications in the early phase by affecting the vascular wall and pericytes. In this context, AGE-2 might take part in development of dementia triggered by cerebral pericyte loss for vascular dementia and neuronal cell apoptosis for AD at the beginning of the disease.

Effect of AGEs on Primary Cortical Neuronal Cells

Many available reports indicate that AGEs are involved in diabetic complications[33,82-85] and other age-related diseases such as inflammation,[86] atherosclerosis,[87-90] and cancer.[30,91-93] AGEs are also implicated in the pathogenesis of AD.[23,65,94-98] We investigated which types of AGEs trigger the development of AD pathology using primary cortical neurons (Figure 2).[26,99] Cell viability was dramatically decreased by the addition of AGE-2, which is a TAGE. Moreover, the neurotoxic effect of AGEs fractions in the serum of diabetic patients undergoing hemodialysis was recovered only upon preincubation with anti–AGE-2 antibody, suggesting that AGE-2 is toxic to cell viability and actually exists in the serum of the diabetic patients. These results indicated that TAGE might show drastic neurotoxicity and cause development of the neurodegenerative disease directly.

The role of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in apoptosis has been described in neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and AD.[100-102] Translocation of the enzyme from the cytosol to the nucleus is a critical step in the induction of apoptosis in neuronal cells.[103-106] We have found that GAPDH activity is reduced by TAGE without a change in caspase activity.[26,99] Although the mechanism of the reduction by TAGE is not clear, the decrease of GAPDH activity leads to an increase of intracellular glyceraldehyde concentration and AGE-2 produced in a vicious cycle. AGE-2 thus may be a general causative agent for development of neurodegenerative disease. AGEs and their

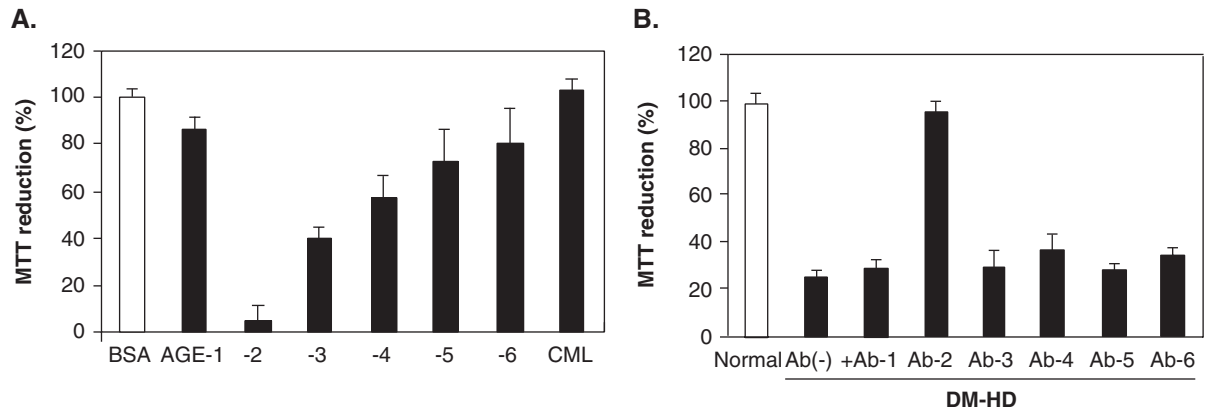

Figure 2. Synthetic advanced glycation end products (AGEs) and serum AGEs from diabetic patients induce neuronal cell death in cultured cortical neurons. (A) Cell viability of cortical neuronal cell after addition of BSA (open bar) or various types of AGEs (filled bars). (B) Neutralization experiments in preincubation with various types of anti-AGEs antibodies and serum AGEs fractions prepared from normal controls (open bars) or diabetic patients on hemodialysis (DM-HD; filled bars). Both experiments are examined by the MTT assay. BSA = bovine serum albumin; Ab-1 = anti–AGE-1 antibody; Ab-2 = anti–AGE-2 antibody; Ab-3 = anti–AGE-3 antibody; Ab-4 = anti–AGE-4 antibody; Ab-5 = anti–AGE-5 antibody; Ab-6 = anti–AGE-6 antibody; MTT = 3-(4,5-dimethylthiazolyl-2-γ)-2,5-diphenyltetrazolium bromide.

precursors (MGO and GO) may increase the aggregation and cytotoxicity of intracellular Aβ carboxy-terminal fragments.[107] Taken together, these considerations underscore the premise that AGEs may be central to the exacerbation of dementia and enhanced predilection of stroke. In this context, both AGE-2 and Aβ are signal transduction ligands of RAGE. So, the above discussed observations suggest the possibility that AGEs, especially AGE-2, are one of the missing links between AD and DM.

Accumulation of AGEs in the Human Brain

The possibility of the involvement of glycation in AD was first suggested in several reports published successively between 1994 and 1995.[23,25,108,109] Senile plaques and NFTs were positively stained with antipyrraline and antipentosidine antibodies.[108] Sasaki et al reported that senile plaques, even diffuse or primitive ones, were positively stained by an antiserum against glucose-derived AGEs (its antiserum could partially recognize protein-bound CML structure).[94,110] The most prominent species of AGEs in tissues, CML adducts, are found at the highest levels in the hippocampus, followed by the cornu ammonis regions. Interestingly, AD patients with DM showed enhanced formation of CML, possibly because of increased levels of glucose and enhanced oxidative stress.[111,112] Many researchers have reported that CML is the dominant epitope recognized by several AGEs antibodies and have suggested that CML is a major immunogenic structure on the surface of AGE proteins. The fact that CML is formed during both glycoxidation and lipoxidation reactions raises some questions about the specificity of many anti-AGEs antibodies and antisera. CML can be formed from the precursors glyoxal and glycolaldehyde by an intramolecular Cannizzaro reaction, a process that is largely independent of glucose autoxidation.[19] The concept that CML is a marker of oxidation rather than glycation has recently received support.

Recently, our studies have suggested that there is a role for AGEs and RAGE, but not CML, in AD.[110] We showed that Aβ-, AGE-1–, and RAGE-positive granules were present in the perikaryon of hippocampal neurons in AD and DM patients. In AD brains, most astrocytes (approximately 70%-80%) contained both AGE-1– and RAGE-positive granules, and their distribution was almost the same, while fewer astrocytes contained Aβ-positive granules (approximately 20%-30%). This finding suggests the presence of glycated proteins other than Aβ. Another of our studies showed that AGE-2 also exists in AD brains.[113] The localization of AGE-2 was mainly in the perikarya of neurons, and the staining pattern was powdery, differing from the dot-like pattern of AGE-1 staining. On the other hand, astrocytes stained weakly with anti–AGE-2 antibody when compared to anti–AGE-1 antibody. In AD

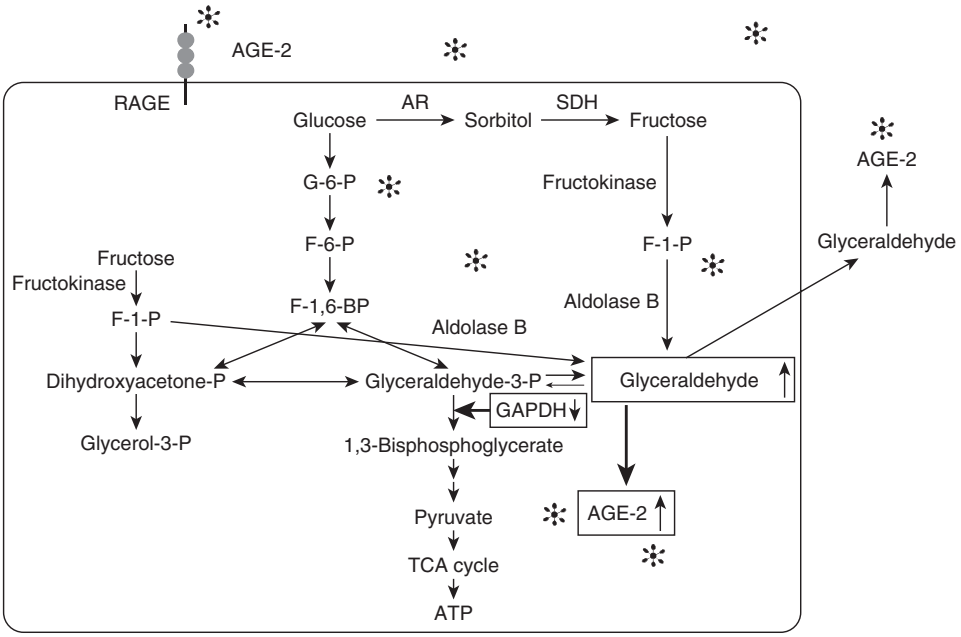

Figure 3. Biosynthesis of glyceraldehyde-derived AGEs (AGE-2). AGE-2 = glyceraldehyde-derived advanced glycation end product; RAGE = receptor for AGEs; AR = aldose reductase; SDH = sorbitol dehydrogenase; GAPDH = glyceraldehyde-3-phosphate dehydrogenase.

brains, many senile plaques were detected by Aβ immunostaining. The AGE-1 antibody also reacted with the senile plaques, mainly the amyloid core, but the AGE-2 antibody showed no immunoreactivity with the plaques. AGE-1 was present at both the intracellular and extracellular sites, while AGE-2 was detected only intracellularly. Protein cross-linking by AGEs structures results in the formation of protease-resistant aggregates. Such protein aggregates may interfere with both axonal transport and intracellular protein traffic in neurons.

Production Route of TAGE In Vivo

As shown in Figure 3, glyceraldehyde is a precursor of AGE-2 that is considered to form by 3 pathways[22,99,114]: (1) glycolytic pathway, (2) polyol pathway, and (3) fructose metabolic pathway. (1) The glycolytic intermediate glyceraldehyde-3-phosphate is normally catabolized by the enzyme GAPDH. As mentioned above, the addition of AGE-2 to neuronal cell cultures caused a decrease in GAPDH activity. This suggests that the intracellular concentration of glyceraldehyde is increased and may further accelerate AGE-2 production and enhance cytotoxicity by a feed-forward mechanism. (2) In hyperglycemic conditions, an increased intracellular glucose concentration stimulates the polyol pathway to accelerate fructose production in insulin-independent tissues such as brain and nerve tissue, kidney, lens, and red blood cells. (3) Another common sugar in the diet is fructose, which is a component of sucrose, or table sugar. Fructose may be metabolized by 2 pathways in cells. It may be phosphorylated by hexokinase, an enzyme that is present in all cells; however, hexokinase has a strong preference for glucose, and glucose, which is present at about a 5 mM concentration in blood, is a strong competitive inhibitor of the phosphorylation of fructose. The other pathway of fructose metabolism involves fructokinase and is especially important in the liver after a meal. In the liver, fructose is phosphorylated to fructose-1-phosphate (F-1-P) by a specific kinase, and liver aldolase, called aldolase B, can cleave F-1-P. In this case, the products are dihydroxyacetone phosphate and glyceraldehyde. Since fructokinase is found in the liver, kidney, intestine, and gut, but not in other tissues, glyceraldehyde might be expected in these tissues.[115] Newly synthesized glyceraldehyde can be transported or can leak passively across the plasma membrane. It can react nonenzymatically with proteins to lead to accelerated formation of AGE-2 in both intracellular and extracellular regions.

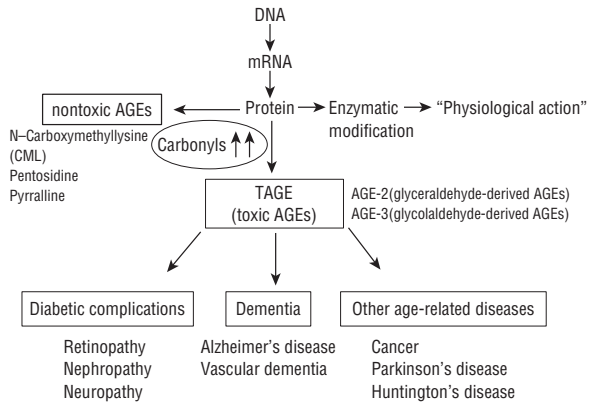

Figure 4. Toxic advanced glycation end-products theory in age-related disease

TAGE Theory in AD

It has been reported that nontoxic AGEs such as CML, pyrraline, and pentosidine are colocalized in Aβ plaques and NFTs, suggesting a role of AGEs in the pathogenesis of AD.[116,117] On the other hand, TAGE, that is, AGE-2, is immunohistochemically detected mainly in the cytosol of neurons of the hippocampus and parahippocampal gyrus but not in the senile plaques of brains in AD patients.[113] Also, TAGE are detected at both intracellular and extracellular sites. These results indicate that the distribution of TAGE differ from that of nontoxic AGEs. The toxic effect of TAGE on neuronal cells is likely a direct event by induction of apoptosis from the early phase of AD development. It is possible that accumulation of the nontoxic AGEs' colocalization with Aβ in senile plaques might inhibit internalization of Aβ in the AD brain. Because nontoxic AGEs have no direct effect on neural cells, they may accumulate to appreciable degrees in healthy subjects.[98] The direct neurotoxicity of TAGE, on the other hand, will stimulate the development of AD.

These results indicate that of the various types of AGEs structures that can form in vivo, TAGE, but not nontoxic AGEs, are likely to play an important role in the pathophysiological processes associated with AGEs formation. TAGE are involved in the pathogenesis of diabetic retinopathy and nephropathy, especially at an early stage of disease development. In retinal pericytes, the cytopathic effects of TAGE, but not those of AGE-1 or CML, were significantly enhanced by overexpression of the RAGE. TAGE induction of apoptosis in Schwann cells may play a critical role in the development of diabetic neuropathy. We postulate that nontoxic AGEs structures may be physiologically relevant mechanisms for averting potentially damaging consequences of the advanced glycation process.

Conclusion

TAGE have been shown to be involved in the pathogenesis of AD. While the precise structure of AGE-2 remains to be determined, our best evidence to date is that AGE-2 forms by the rearrangement of glyceraldehyde addition products.[42] Recent studies have demonstrated that glyceraldehyde-derived and glycolaldehyde-derived AGEs have a pyridinium moiety,[118-120] suggesting that a specific and common chemical scaffold may be responsible for the cytotoxicity of TAGE. TAGE stimulate the growth and migration of cancer cells,[30,121] and they may also cause other neurodegenerative disease (Figure 4). Pathophysiological and structural studies of TAGE will give us valuable information regarding the development of age-related diseases and their prevention.

Numerous blood and CSF tests have been proposed for early detection of AD.[122,123] However, not all results are consistent.[124] Given the multiple etiologies and pathological process of AD, more than 1 biological marker will probably be necessary for the early diagnosis of this disorder. We would like to hypothesize that serum or CSF levels of TAGE could become a promising biomarker for early detection of AD. We also propose possible means of testing this hypothesis. Are the concentrations of TAGE in serum or CSF elevated early in the course of dementia? Are these levels correlated with disease severity and progression, especially in patients with DM? These clinical studies may clarify the utility of serum or CSF levels of TAGE as biomarkers for AD and might enable more effective diagnosis and treatment of patients with this devastating disorder.

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