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REVIEW ARTICLE

Advanced glycation endproducts and their pathogenic roles in neurological disorders

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Abstract Glycation is implicated in neurological disorders. In some cases it plays a key role in the pathogenesis, in others it plays a co-adjuvant role or it appears as a consequence of degenerative changes and protein accumulation stemming from other pathways. In this work, we attempt to provide a concise, updated review of the major recent findings concerning glycation in neurological diseases. After a short introduction covering advanced glycation endproducts (AGEs) and the receptor for AGEs (RAGE), we will discuss the impact of glycation in central nervous system disorders including Alzheimer's, Parkinson's and Creutzfeldt–Jakob disease, as well as peripheral diabetic polyneuropathies. Therapies directed at lowering the concentrations of RAGE ligands including AGEs, blocking RAGE signaling, preventing oxidative stress or lowering methylglyoxal (MGO) levels may significantly decrease the development of AGE-related pathologies in patients with neurological disorders. Many drugs are on the pipeline and the future clinical trials will reveal if the promising results translate into clinical application.

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Introduction

Glycation is implicated in neurological and neurodegenerative disorders, in some cases it plays a key role in the pathogenesis, in others it plays a co-adjuvant role or it appears as a consequence of degenerative changes and protein accumulation. There are many high-quality reviews of the role of glycation in specific neurological disease and the reader is directed to them (Münch et al. 1997b, 1998; Thome et al. 1996; Thornalley 2002; Ahmed 2005; Cameron and Cotter 1993, 2008; Haslbeck et al. 2007; King 2001; Lukic et al. 2008; Obrosova 2002, 2003, 2009; Sugimoto et al. 2008; Toth et al. 2007a, b). In this work, we attempt to provide a concise, updated review of the major recent findings concerning glycation and neurological disease. After a short introduction covering glycation and advanced glycation endproducts (AGEs) and the receptor for AGEs (RAGE), we will discuss the impact of glycation in central nervous system (CNS) disorders and peripheral neuropathies.

Advanced glycation endproducts

AGEs 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 (MGO) and triosephosphates (Brownlee 1995; Thorpe and Baynes 1996). AGE formation can also commence when amino groups of proteins,

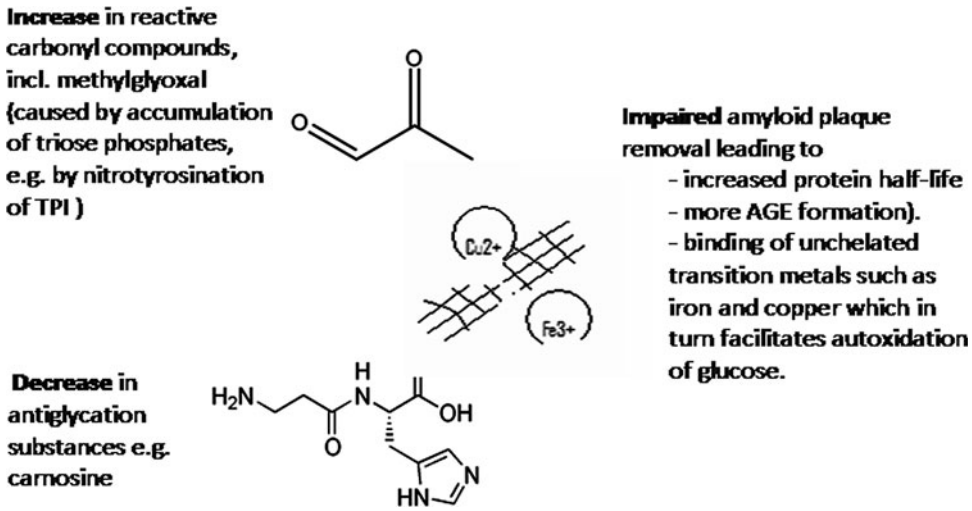

Fig. 1 Factors accelerating the formation of AGEs in Alzheimer's disease. An increase in reactive carbonyl compounds such as MGO, an increase in transition metals such as copper and iron loosely bound to amyloid plaques, a depletion of the antiglycation substance pool (e.g., carnosine) and defective Aβ clearance or degradation might all contribute to higher AGE levels in brains of AD patients

particularly the N-terminal amino group and side chains of lysine and arginine react non-enzymatically with these reactive carbonyl compounds (Münch et al. 1999). 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. 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. 2000) (Fig. 1). 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 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 cross-linking of peptides and proteins, leading to protein deposition and amyloidosis. Glycation by glucose and fructose occurs on the N terminus of the protein and the side chains of lysine, arginine, but also on cysteine and histidine. Crosslinking of protein-AGEs to dipeptides with free side chains and blocked N termini occurs preferentially to arginine and tryptophan (Münch et al. 1999).

AGEs in aging

In the 1970s and 1980s, Monnier and Cerami (1981), 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. 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).

Direct toxic effects of AGEs

AGEs have been shown to be more than a harmless post-translational protein modification. One of the proposed mechanisms of AGE-induced damage is reactive oxygen species (ROS), particularly superoxide and hydrogen peroxide released by AGEs (Carubelli et al. 1995; Ortwerth et al. 1998; Muscat et al. 2007). 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 non-glycated 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 (Wolff et al. 1989).

Since the oxidation of glycated proteins, as shown above 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, *N*(epsilon)-(carboxymethyl) lysine (CML) (Gasic-Milenkovic et al. 2001). Moreover, a similar effect can be observed with MGO-derived BSA-AGEs. The effect of different BSA-AGEs (derived from MGO) 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). The cytotoxic effects of AGEs could 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, it was shown that AGEs [BSA-AGE and *β*-amyloid-AGE (A*β*-AGE)] persistently increase the ratio of oxidized to reduced glutathione (GSH) in a dose- and time-dependent manner in SH-SY5Y neuroblastoma cells (Deuther-Conrad et al. 2001). The AGE-induced increase in oxidized glutathione could be prevented by the radical scavengers *N*-acetylcysteine, α-lipoic acid and 17*β*-estradiol or by application of catalase, indicating that superoxide and hydrogen peroxide production precedes the AGE-mediated depletion of GSH (Deuther-Conrad et al. 2001). In addition, AGEs decrease glucose consumption, ATP levels and mitochondrial activity measured by MTT assay (Kuhla et al. 2004).

Activation of macrophages and microglia by AGEs: the receptor for advanced glycation endproduct (RAGE) pathway

The activation of microglial RAGE by many of its ligands, including AGEs and A*β*, results in the release of proinflammatory mediators such as free radicals and cytokines (Berbaum et al. 2008). AGEs, for example, can induce the expression of proinflammatory cytokines through nuclear factor κB (NF-κB)-dependent pathways via its receptor

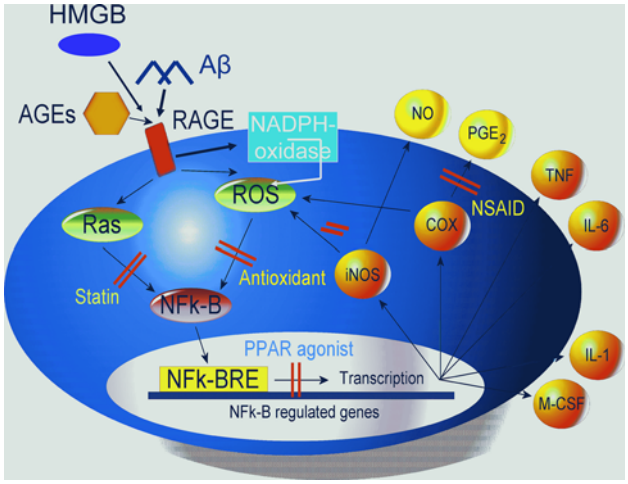

Fig. 2 Proinflammatory NF-κB signaling through RAGE. Activation of the RAGE activates the transcription factor NFκ-B via Ras and redox-sensitive signaling pathways, leading to transcription of genes coding for inducible nitric oxide synthase and a variety of cytokines including IL-1, IL-6 and TNF-α

RAGE (as depicted in Figs. 2, 4). It was 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. 2003). Interestingly, the combination of A*β* 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). Using a cytokine bead array, the BSA-AGE-induced expression of selected cytokines/chemokines in two murine cell lines, RAW 264.7 macrophages and N-11 microglia was analyzed. It was shown 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 Interestingly, MCP-1 was also constitutively expressed by unstimulated cells, although at a lower levels. These 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).

Glycation and other CNS disorders

Most of the early and present research on glycation and disorders of the CNS has been conducted in connection with Alzheimer's disease. However, more recent work has also shown a role of AGEs in other serious debilitating diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and others. There is an emerging

picture for a role for RAGE and sRAGE in these disorders, and some promising, though still preliminary work suggests sRAGE maybe have predictive value in the most common CNS disorder: stroke. A clear example of how important AGEs may be in neuronal disorders is triose phosphate isomerase (TPI) deficiency. TPI is a rare disorder that models the impact of increased flux of MGO in neuronal function and survival, and serves as an exaggerated example of how excessive AGE accumulation leads to neuronal death. In this section we will therefore discuss, in sequence, Alzheimer's disease, TPI, ALS, MS and the other neurodegenerative diseases.

Alzheimer's disease and the involvement of AGEs

The involvement of AGEs in brain aging and, in an accelerated fashion, in neurological disorders was first proposed in the mid-1990s for Alzheimer's disease (Yan et al. 1994; Vitek et al. 1994; Smith et al. 1995). Distribution of AGEs has since 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 (NFTs) 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.

Intracellular AGE deposits

In humans, AGEs are localized in pyramidal neurons, exhibiting a granular, perikaryonal distribution (Fig. 3). These pyramidal neurons appear to selectively accumulate AGE-containing vesicles in an age-dependent manner starting in the second decade of life (Takedo et al. 1996). High-resolution immunochemistry suggests that AGEs accumulate in endosomes or lysosomes, and that they appear to be a constituent of lipofuscin (Horie et al. 1997; Anzai et al. 2006). In the AD brain, extraneuroperikaryal AGE (CML and pentosidine) deposits are co-localized with glial fibrillary acidic protein-positive astrocytes, as depicted in Fig. 3 (Horie et al. 1997). In a further study, the

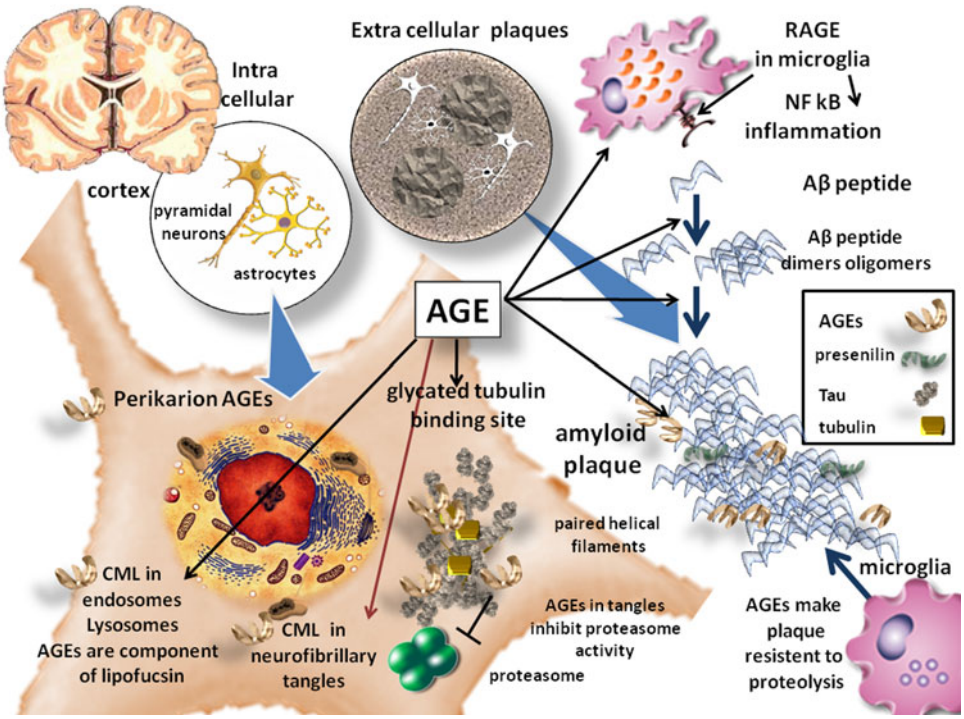

Fig. 3 AGEs in AD AGEs are associated with both pathognomonic histological hallmarks of AD: intracellular NFTs (composed of modified tau—a cytoskeletal protein—and tubulin) and extracellular amyloid plaques. Pyramidal neurons in AD typically display perikarion accumulation of AGEs, which are also found in endosomes and lysosomes, as shown by histo- and cytochemistry probing with anti-CML antibody. Glycation of the tubulin binding site of tau (a component of the cytoskeleton) may produce its detachment from the normal structural scaffold and may be implicated in NFT formation. As depicted on the *top right*, an increased load of AGEs activates the RAGE pathway in microglia, which, as described in the text and depicted in Fig. 2 leads mainly to NF-κB responses, that, when perpetuated are damaging to cells. At the extracellular level (*right side*) the amyloid plaque stems from the precipitation of dimers and oligomers of Aβ-peptides, together with other proteins, including presenilin

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 was compared. 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 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 was 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 hyperphosphorylated tau, suggesting a link between AGE accumulation and the formation of early NFTs (Lüth et al. 2005).

NFTs 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 consists 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. 1994; Smith et al. 1994). 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 (shown in Fig. 3) (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 play a role in stabilizing PHF aggregation, leading to tangle formation in AD, as depicted in Fig. 3. 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 and Perry 1994). 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 (Stolzing et al. 2006), as shown in Fig. 3.

Extracellular AGE deposits

Increased extracellular AGE formation has been demonstrated in amyloid plaques in different cortical areas, as depicted on the right side in Fig. 3. In another immunohistochemical study, vascular walls in amyloid angiopathy were not labeled 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 (Sasaki et al. 1998). In AD, CML was found to be co-expressed with Tau protein, showing the similar NFT shape as in neuritic plaques, but not in the core of amyloid plaques (Castellani et al. 2001; 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, as depicted in Fig. 3.

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. Nucleation-dependent polymerization of Aβ peptide, the major component of plaques in patients with AD, is significantly accelerated by cross-linking through AGEs (Loske et al. 2000). These in vitro experiments using synthetic Aβ peptide and glucose or fructose show that the 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, as illustrated on the right side of Fig. 3.

Based on these results, it was speculated whether metal chelators were able to prevent formation of AGEs or their precursors. One study investigated the effects of a metal chelating agent (TE) hydrochloride on the levels of methylglyoxal (MG) and 3-deoxyglucosone (3-DG) in lenses from streptozotocin-induced diabetic rats. Lens MG and 3-DG levels were significantly higher in diabetic rats than non-diabetic controls, and TE significantly decreased the level of these compounds in the diabetic rats. Lens

argpyrimidine was also increased in diabetic rats as compared with controls and was significantly reduced by TE. The results indicate that transition metals play a significant role in the formation of MG and 3-DG via oxidative stress, and the increase in AGEs and their precursors can be normalized by the metal chelating agent, trientine (TE) hydrochloride (Hamada et al. 2005).

Factors promoting AGE formation in neurological disorders including AD

AGE production is increased in hyperglycemic 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 patients with age-related neurological diseases including AD. 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 (MGO) as a consequence of triose phosphate accumulation, resulting from disturbed glucose metabolism, e.g., by inhibition of mitochondrial respiration; (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 (Fig. 1).

MGO is a reactive α-oxoaldehyde and a physiological metabolite generated from both enzymatic and non-enzymatic reaction pathways. Non-enzymatic formation of MG has been found to occur from glycerone phosphate and glyceraldehyde 3-phosphate. The rate at which these processes of MGO formation are thought to occur has been estimated to be 0.89% of flux of glucotriose through glycolysis (Thornalley 1988).

The increase of MGO 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 et al. 2003). 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). It has also 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). Furthermore, AGEs could contribute to the inability of microglia to clear plaques by introducing crosslinks to Aβ and other plaque-associated proteins which make it difficult to take up and degrade Aβ by inhibiting lysosomal proteases such as cathepsin D, as we illustrate in Fig. 3, right lower corner (Miyata et al. 1997; Sebekova et al. 1998).

Glycation and TPI deficiency

TPI deficiency is a rare disorder that models the impact of increased flux of MGO in neuron function and survival (Ahmed et al. 2003; Gnerer et al. 2006; Orosz et al. 2001). TPI is an enzymopathy of glycolysis, leading to hemolytic anemia and associated with severe multisystemic disorders (neuropathy, myopathy). It has an autosomal recessive inheritance (Schneider 2000). As shown in Fig. 4, TPI deficiency impairs the conversion of dihydroxyacetone phosphate (DHAP) to glyceraldehyde-3-phosphate, which then follows glycolysis. The accumulation of DHAP leads to production of excess MGO (Ahmed et al. 2003). This, in turn, can deplete GSH (glyoxalase I cycle) form adducts with proteins damaging them and increase ROS. In erythrocytes, which do not have mitochondria and only metabolize glucose in anaerobiosis, this has serious consequences (Orosz et al. 2001; Wilmshurst et al. 2004). There is an early-onset of chronic hemolytic anemia, in general, during the neonatal stage (Arya et al. 1996). In neurons, the defect shunts trioses out of the normal pathway and deprives neurons from part of that energy source. Neurological involvement is progressive and starts between 6 and 30 months of age. This leads to severe complications such as paralysis of the diaphragm, and severe cardiac failure that is the main cause of patient's early death during

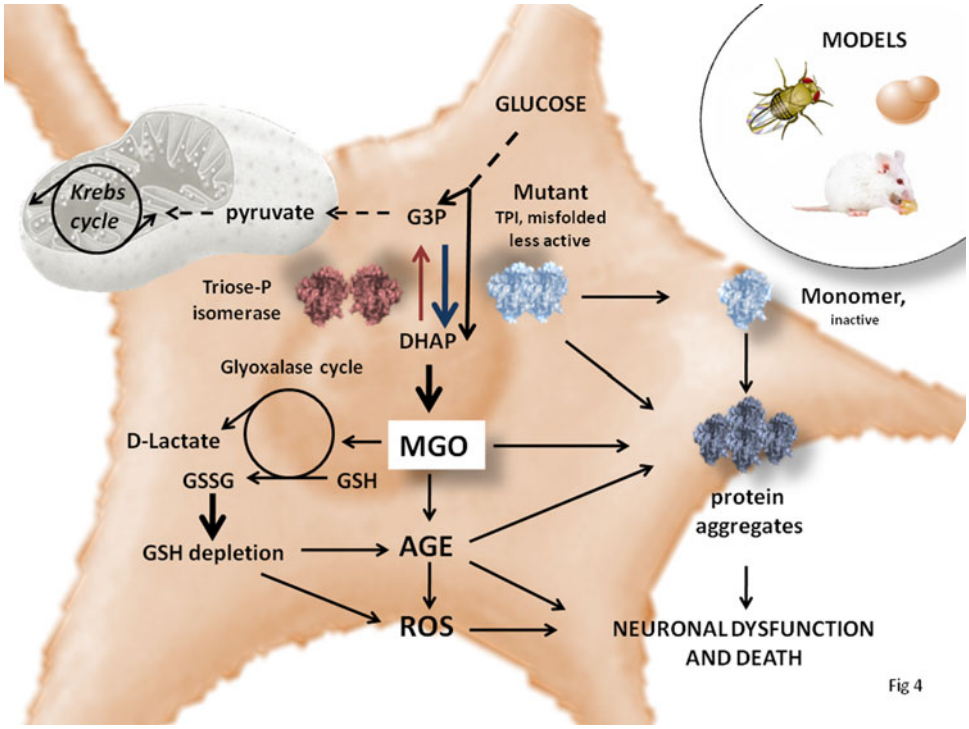

Fig. 4 Triose phosphate isomerase deficiency (TPI): a rare disorder that models the impact of increased flux of MGO in neuron function and survival. As shown, TPI deficiency impairs the conversion of dihydroxyacetone phosphate (DHAP) to glyceraldehyde-3-phosphate. The accumulation of DHAP leads to production of excess MGO. This, in turn, can deplete GSH (glyoxalase I cycle); can form adducts with proteins and damage them and both pathways increasing ROS. In neurons, the defect shunts trioses out of the normal pathway and deprives the neuron from part of that energy source. Neurological involvement is progressive and starts between 6 and 30 months of age. TPI is the final result of several point and nonsense mutations. As shown, studies in eukaryotic models such as yeast, mice and the fruit fly support the contention that, in most cases, the mutation leads to a form of the enzyme that does not dimerize properly. This leads to a poorly active enzyme that tends to dissociate and aggregate. The aggregation per se, coupled to the AGE production, the ROS and the energy shunting all conspire against the function of the neurons, with catastrophic consequences

childhood (Schneider 2000). TPI is the final result of several point and nonsense mutations. As shown in the figure, studies in eukaryotic models such as yeast, mice and the fruit fly, support the contention that, in most cases, the mutation leads to a form of the enzyme that does not dimerize properly (Celotto et al. 2006; Olah et al. 2002), resulting in a poorly active enzyme that tends to dissociate and aggregate. The aggregation per se, coupled to the AGE production, the ROS and the energy shunting all conspire against the function of the neurons, with catastrophic consequences. TPI can be considered, in a way, a model and a proof of principle that illustrates the deleterious consequences of increased flux of MGO for neuronal function and integrity (Ahmed et al. 2003).

Glycation and multiple sclerosis (MS)

Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting CNS axons. It starts with sensory and motor deficits in some cases followed by complete remission and a secondary, progressive phase during which the neurological deficits increase steadily. The underlying molecular mechanisms responsible for disease progression are still unclear. The defect targets oligodendrocyte myelin and there is supporting evidence of oxidative stress with production of ROS in the CNS of MS patients (Langemann et al. 1992). Even if an increase of AGE products has not been found in patients with MS compared to controls (Kalousova et al. 2005), an up-regulation of the RAGE receptor in patients with MS and animal models of MS has been reported (Andersson et al. 2008).

As described earlier, RAGE is a pleiotropic transducer of signals coming from multiple ligands: calgranulins, Aβ, advanced glycation, and pro-inflammatory molecules including the high mobility group box 1 (HMGB1) (Rong et al. 2005; Srikanth et al. 2009), and many others. RAGE has an important role in promoting inflammatory processes through interaction with leukocytes and endothelial cells triggering the activation of the NF-kB and the recruiting of inflammatory cells (Chavakis et al. 2003). These pro-inflammatory processes when perpetuated are damaging to cells, and more so to neurons that, for the most part, do not reproduce and accumulate damage (Chavakis et al. 2003).

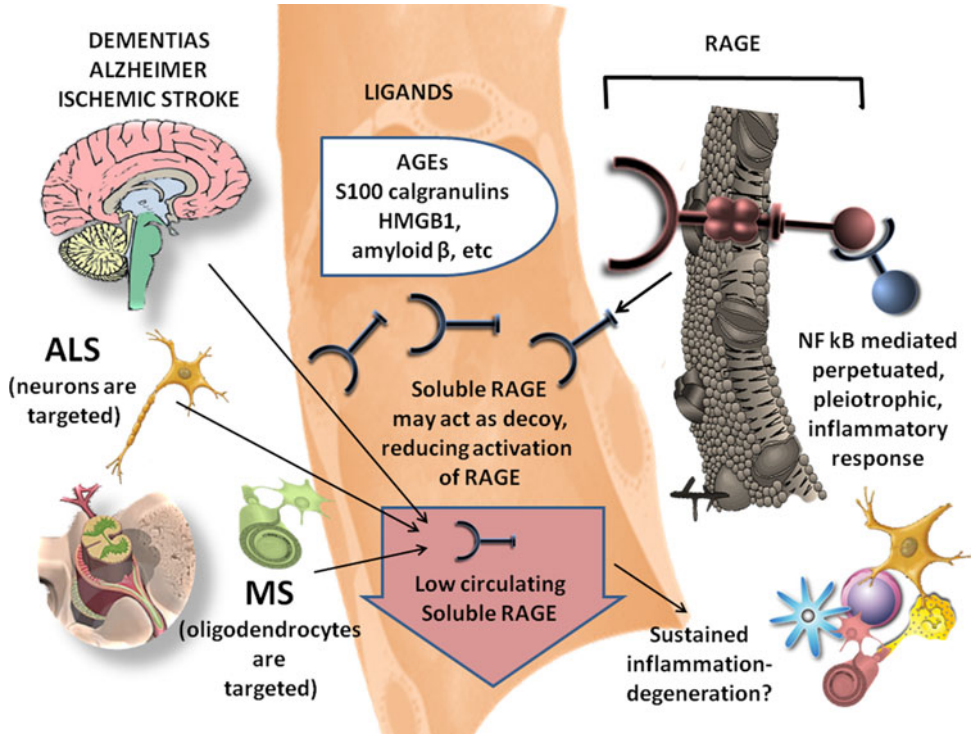

Fig. 5 Receptor for advanced glycation end products (RAGE) and its circulating, soluble form in central neurological disorders. RAGE is a pleiotropic transducer of signals coming from multiple ligands stemming from inflammation, calgranulins, *β*-amyloid, advanced glycation and many others. A soluble form (sRAGE) of this receptor is found in the bloodstream. It is believed that this form may act as a decoy or competitive inhibitor of the binding of the ligands to the cell receptor, therefore preventing excessive stimulation of the NF-κB responses. Research conducted over the past few years converge to show a role of sRAGE in disorders of the central nervous system. As shown in the *left*, studies on encephalic disorders in humans have shown that sRAGE levels are lower in dementias including Alzheimer's disease and in ischemic stroke as well. Patients with either amyotrophic lateral sclerosis (ALS)—which affects mainly neurons in the spinal chord—or with multiple sclerosis (MS), where the main target is the oligodendrocyte's myelin, display reduced concentrations of sRAGE in plasma. These findings suggest that in these conditions there is a larger load of ligands that overwhelms the sRAGE scavenging pathway and/or there is a defect in its production by cells which, in turn, allows for more ligand interaction with neurons and glia, leading to sustained inflammation and degeneration

Up-regulation of the RAGE receptor and its ligands have been found in degenerative disease of the nervous system and also in acute brain injury. In fact, Anderson found by studying human MS lesions from autopsies that RAGE receptors were expressed in inactive MS lesion, but there was an increase expression in active lesions. This was also the case when they studied active lesions in the animal model of MS, experimental autoimmune encephalomyelitis (EAE). There was also an increased expression of RAGEs in the cells from the CSF of MS patients. The authors hypothesize that a significant expression of RAGE and one of its ligands HMGB1 in microglia could amplify the inflammatory response in MS (Andersson et al. 2008). Their findings support previous reports where the interaction between RAGE and HMGB1 were implicated in the secretion of cytokines and of leukocyte recruitment, thus perpetuating the inflammatory process (Fiuza et al. 2003; Chavakis et al. 2003).

In peripheral nerve injury, however, the initial increase expression of HMGB and RAGE in the site of damage with initiation of an inflammatory process would favor the phagocytosis of myelin debris which provides an adequate environment for outgrowth of nerve fibers and remyelination (Rong et al. 2004). This implies a difference in function of HMGB1–RAGE interaction in CNS versus PNS.

A soluble form of RAGE (sRAGE) is found in the bloodstream. It represents the cleaved extracellular segment or a spliced form of the receptor. As shown in Fig. 5, it is believed that this form may act as a decoy or competitive inhibitor of the ligands binding to the cell receptor, therefore, preventing excessive stimulation of the NF-κB responses (Sakaguchi et al. 2003). Sternberg et al. (2008) found that the levels of sRAGE decreased in the plasma of patients with MS and the decrease had a direct relationship with disease duration and severity, with lower levels of sRAGE present in those patients with more severe forms of the disease (Sternberg et al. 2008). Because other studies had reported low levels of sRAGE in other neurological disease, the authors suggest sRAGE levels as possible markers of neurological injury. As shown to the left of

Fig. 4, studies on CNS disorders in humans have shown that sRAGE levels are also lower in dementias including AD and in ischemic stroke, where some predictive value has been reported. In the other major degenerative disorder of the CNS, amyotrophic lateral sclerosis (ALS), which affects mainly neurons, reduced concentrations of sRAGE in plasma have been reported, as discussed below. These findings suggest that in these conditions there could be a larger load of ligands that overwhelm the sRAGE scavenging pathway and/or a defect in its production by cells, which, in turn, allows for more ligand interaction with neurons and glia, leading to sustained inflammation and degeneration.

Glycation and ALS

ALS is a progressive neurodegenerative disease of the lower motor neurons in the spinal cord and brainstem leading to paralysis of the voluntary muscles of the body. Speech and respiration are also affected. Even if the mechanisms that produce the disease are still under intense study and 90% of the cases are sporadic, important facts regarding the pathogenicity in the 10% of cases that are hereditary in origin have been elucidated. In these inherited cases there is a mutation in the enzyme copper–zinc superoxide dismutase (SOD1). Since SOD1 is one of the enzymes involved in the catalytic quenching of superoxide radicals, oxidative stress may be important in the initiation and progression of the disease (Kikuchi et al. 2003). The main pathological event is the accumulation of neurofibrillary-derived Lewy-body-like hyaline inclusion in the neuronal cytoplasm in both sporadic and inherited cases of ALS (Chou et al. 1998; Kato et al. 2000; Gros-Louis et al. 2006; Pasinelli and Brown 2006). An increased susceptibility of SOD1 to glycation was observed due to the presence of several lysine and arginine residues in the primary structure of the enzyme (Takamiya et al. 2003). AGE formation of SOD1 composing the neuronal deposits may amplify their aggregation and produce a more marked toxicity.

The presence of CML and non-CML AGEs were shown in the anterior horn motor neurons and microglia in the spinal cord of patients with ALS (Kikuchi et al. 2002). The same results were obtained by studying the astrocytes and spinal cord neurons immunoreactivity to CML in patients with the SOD1 mutation and mutant SOD1 transgenic mice compared with controls (Shibata et al. 2002a). Patients affected by sporadic ALS presented the same pattern of CML elevation in spinal cord neurons and astrocytes with increased levels of CML and pentosidine (Shibata et al. 1999, 2002b). All of these findings point to an involvement of glycation and oxidative stress in the initiation and possibly the progression of ALS. Their studies seem to point to a difference between sporadic and inherited ALS. Protein glycation, but not lipid peroxidation, was enhanced in ALS patients with an SOD1 mutation but in sporadic ALS, both lipid peroxidation and protein glycoxidation were enhanced in spinal cord motor neurons and glial cells (Shibata et al. 2002a). In a further study, sRAGE levels were measured in the serum of ALS patients, and it was found that sRAGE levels were significantly decreased in ALS compared to the control group (Ilzecka 2009), as we depict in Fig. 5. They postulate a relationship between serum levels of sRAGE and disease. Other authors also postulate that sRAGE could prove beneficial to counter the pro-inflammatory effects of RAGE activation by consuming RAGE ligands (Sakaguchi et al. 2003).

Glycation and other neurodegenerative disorders

Glycation and glycoxidation have been implicated in the pathogenicity of Parkinson's disease. Parkinson's disease is a degenerative disease of the nervous system affecting the dopaminergic neurons of the substantia nigra in the midbrain. The disease is progressive and presents with tremor and paucity of movements, muscle rigidity and a characteristic shuffling gait among other symptoms. There is accumulation of aggregates of an intracellular protein, α-synuclein (α-syn) and Lewy bodies that trigger neuronal death (Castellani et al. 1996). Decreased levels of intracellular GSH (Sian et al. 1994), modification of Lewy bodies by AGEs (Münch et al. 2000), and altered RAGE expression (Dalfo et al. 2005), all of which have been found to contribute to the damaging and eventual death of dopaminergic neurons.

Creutzfeld–Jakob disease (CJD) is characterized by the intracellular accumulation of aggregates of an abnormally folded prion protein. AGE proteins and RAGE have also been found in brain tissue from patients affected by CJD (Sasaki et al. 2002). It is proposed that AGE formation could have a role in the abnormal folding of prion proteins, their aggregation and the progression of the disease (Vicente Miranda and Outeiro 2010).

Does AGE formation link diabetes to Alzheimer's disease and other neurodegenerative diseases?

The deleterious effects of diabetes mellitus on the retinal, renal, cardiovascular, and peripheral nervous systems are widely acknowledged. More recently, it has become more and more evident that diabetes also exerts a pathogenic influence on the CNS. For example, both type 1 and type 2 diabetes mellitus have been associated with reduced

cognitive performance (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 incident 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 all play significant roles. Glycation as a biochemical link between diabetes mellitus and Alzheimer's disease has been suggested about 15 years ago in landmark papers by Smith et al. (1996a, b).

The role of AGEs in the development of neuronal complications of diabetes such as polyneuropathy and dementia has recently attracted considerable attention (Toth et al. 2007a). It was hypothesized that cognitive dysfunction in vascular dementia may relate to microvascular disease 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 *N*ε-(carboxymethyl)-lysine (CML), the most abundant AGE. It was tested if, 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 is related to cognitive impairment and a history of diabetes (Southern et al. 2007).

"Insulin resistance" in the brain is another possible pathway by which Type 2 diabetes mellitus 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 cerebrospinal fluid insulin under fasting conditions (Hoyer 1998, 2004; Salkovic-Petrisic and Hoyer 2007; Fujisawa et al. 1991). 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).

In Parkinson's disease, the association between diabetes preceding Parkinson's disease (PD) and PD was studied in a case–control study. Surprisingly, the authors found an inverse association between PD and diabetes preceding PD onset in all groups stratified by gender, age at PD onset, body mass index, smoking habit, alcohol and coffee consumption. Multivariate analysis yielded the same findings after controlling for the variables (adjusted OR 0.4, 95% CI 0.2–0.8) (D'Amelio et al. 2009).

Glycation and peripheral nervous system disorders: diabetic neuropathy

The classical and frequent disorder of the peripheral nervous system strongly linked to hyperglycemia is diabetic neuropathy. There are many excellent reviews on the different aspects of the pathogenesis of diabetic neuropathy, and the reader is referred to them for detailed information (Obrosova 2009; Cameron et al. 2001; Said 2007; Vinik et al. 2006). Diabetic neuropathy is one of the most prevalent complications of diabetes mellitus (DM). Vascular changes related to DM lead to endothelial dysfunction and are key mechanisms proposed to have an important causative role in the pathogenesis of neuropathy (Cameron et al. 2001). A number of factors have been implicated in these changes: increased aldose reductase activity, activation of protein kinase C, oxidative-nitrosative stress, changes in arachidonic acid and prostaglandin metabolism, impaired neurotrophic support, activation of the poly (ADP-ribose) polymerase-1, mitogen-activated protein kinase (MAPK) activation, NF-kB, activation of cyclooxygenase-2 (COX-2) and glycation (Thornalley 2002; Cameron and Cotter 2008; Cameron et al. 2001; Obrosova 2003; Obrosova et al. 2004; Toth et al. 2007b, 2008). The mechanisms are intricate and complex, but a general picture emerges to make oxidative/nitrosative stress a common link between the different pieces and glycation playing a role in enhancing and/or initiating several of these pathways, as we schematically summarize in Fig. 6. We will concentrate here on the role of glycation and glycoxidation. A recent review by Obrosova (2009) should be consulted for more details on the other implicated factors.

Diabetic neuropathy is a peripheral, distal, bilateral neuropathy affecting both somatic and autonomic nerve fibers and it is the most frequent long-term complication of DM (Yagihashi et al. 2007). Cardiac autonomic neuropathy may contribute to myocardial infarction (and frequently masks the pain, making the patient seek help too late), malignant arrhythmia and sudden death.

Gastroparesis is the most debilitating complication of gastrointestinal autonomic neuropathy. Genitourinary autonomic neuropathy causes erectile dysfunction and neurogenic bladder (Yagihashi et al. 2007). The effect on somatic nerve fibers produces anesthesia and loss of protective sensation which is a key cause for delayed healing in diabetic foot ulcer patients. Hyperglycemia and several

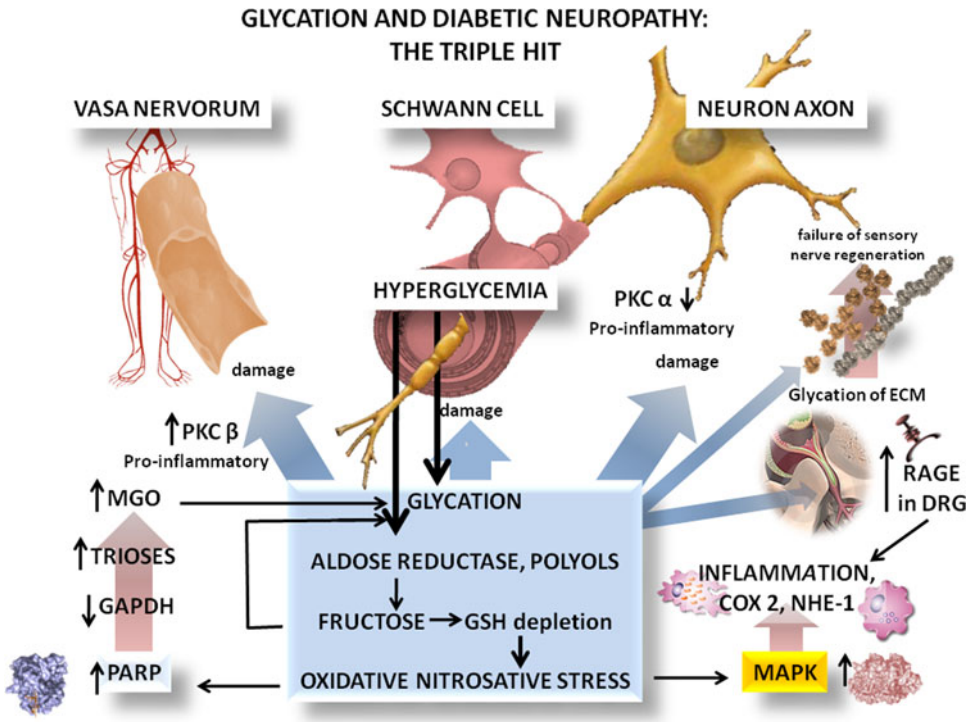

Fig. 6 Glycation and diabetic neuropathy. A better understanding of the role of glycation in diabetic neuropathy can be obtained if one considers that the neural deficit is the consequence of a metabolic shift at three levels: the endothelium of the vasa nervorum, the sensory neuron (dorsal root ganglia) axon and the Schwann cell (glia). The figure depicts some aspects of this triple hit, which has some common pathways in all cells and some particular differences in others. Hyperglycemia leads to polyol and fructose accumulation (fructose been a strong glycating agent), NADPH and GSH depletion and oxidative/nitrosative stress. This, as seen in the *bottom left*, damages DNA, increases poly (ADP-ribose) polymerase (PARP) activity, which inactivates GAPDH, leading to MGO accumulation and more glycation and damage to the type of cells. Protein kinase C-β is activated in the vasa nervorum as a result of these metabolic shifts, which produces inflammatory damage to the endothelium, increased permeability and cell death. Conversely, protein kinase C-α is inactivated in neuronal axons, which has deleterious consequences. Glycation of the extracellular matrix components has been shown to produce failure of nerve regeneration, compounding the problem. Dorsal root neurons RAGE is increased and so are its associated NF-κB responses, that, when perpetuated are damaging to neurons that do not reproduce and accumulate damage. Finally, MAPK pathways are activated, as seen in the *bottom right*, by the same metabolic shifts depicted in the *centre*, resulting in COX 2 activation with strong pro-inflammatory components. Activation of the Na+/H+ exchanger 1 (NHE-1) an integral membrane protein involved in pH regulation also occurs during hyperglycemia in Schwann cells

of its metabolic and cell signaling consequences including AGE accumulation have been linked to impaired diabetic wound healing. This sequence of events, often paired with the concurrent macro- and micro-angiopathy, leads frequently to gangrene. A large body of evidence from in vitro and in vivo studies and also data from studies using anti-AGE agents indicate that AGEs may play a role in the pathogenesis of impaired diabetic wound healing. AGEs affect the wound healing process either directly by their interference with a variety of components involved or indirectly through their association with diabetic neuropathy and/or angiopathy (Huijberts et al. 2008; Peppa et al. 2009).

As previously stated, diabetic neuropathy has a multifactorial origin strongly linked to the effects of hyperglycemia, including glycation. It is thought to occur both from direct hyperglycemia-induced damage to the nerve parenchyma (neurons and supporting glia) and from neuronal ischemia indirectly resulting from hyperglycemia-induced decreases in neurovascular flow. Early vasa nervorum functional changes are caused by the changes in flux of metabolites in DM (Cameron et al. 2001). The delicate balance between vasodilation and vasoconstriction is changed. A better understanding of the pathogenesis of diabetic neuropathy can be obtained if one considers that the neural deficit is the consequence of a metabolic shift at three levels:

1. the endothelium of the vasa nervorum,
2. the sensory neuron (dorsal root ganglia) axon, and
3. the Schwann cell (glia).

Figure 6 depicts some aspects of this triple hit, which has some common pathways in all cells and some particular differences in others. Nerves of human diabetic

subjects contain AGEs in the perineurium, in endothelial cells and pericytes of endoneurial microvessels. Myelinated and unmyelinated fibers contain AGEs localized to irregular aggregates in the cytoplasm and interstitial collagen and basement membranes (Thornalley 2002). High intracellular glucose concentration, in cells that do not depend on insulin for glucose transport, such as neurons, leads to increased formation of MGO, glyoxal, and 3-deoxyglucosone that glycate proteins to form AGEs that elicit intracellular and extracellular effects. Oxidative stress enhances these processes and is, in turn, enhanced by AGE/RAGE interactions, as depicted in Figs. 2 and 6. One strategy to prevent glycation is the use of α-oxoaldehyde scavengers, such as aminoguanidine or tenilsetam (Webster et al. 2005). Other options are high-dose nicotinamide and thiamine therapies to prevent MGO formation. RAGE antagonists are under intensive scrutiny and putative inducers of the enzymatic anti-glycation defense are to be considered in the future.

Hyperglycemia also leads to polyol and fructose accumulation (fructose being a strong glycating agent), NADPH and GSH depletion and oxidative/nitrosative stress (Brownlee 1995). This, as seen in the bottom left in Fig. 6, damages DNA, increases poly (ADP-ribose) polymerase (PARP) activity, which inactivates GAPDH, leading to MGO accumulation and more glycation and damage (Rabbani and Thornalley 2008; Pacher et al. 2005). Protein kinase C-β is activated in the vasa nervorum as a result of these metabolic shifts, which produce inflammatory damage to the endothelium, increase permeability and cause cell death. Conversely, protein kinase C-α is inactivated in neuronal axons, which has deleterious consequences (Sugimoto et al. 2008). Glycation of the extracellular matrix components has been shown to produce a failure of nerve regeneration, compounding the problem, as shown in Fig. 6 (right side) (Duran-Jimenez et al. 2009).

MAPK pathways are also activated, as seen in the bottom right of Fig. 6, by the same metabolic shifts depicted in the centre of the same figure, resulting in COX 2 activation with strong pro-inflammatory results. Activation of the Na+/H+ exchanger 1 (NHE-1) an integral membrane protein involved in pH regulation also occurs during hyperglycemia in Schwann cells (Obrosova 2009).

Dorsal root ganglia neurons express RAGE and respond to the RAGE ligand S100 (Vincent et al. 2007) with similar downstream signaling, oxidative stress, and cellular injury as other diabetic complication-prone tissues, as depicted in Figs. 2 and 4. RAGE-induced phosphatidylinositol-3 kinase activity is associated with the formation of ROS, caspase-3 activation, and nuclear DNA degradation (Haslbeck et al. 2005, 2007). The other associated NF-κB responses when perpetuated are damaging to neurons that do not reproduce and accumulate damage. Activation of NF-kB- and NF-kB-dependent gene expression has been shown to be up-regulated in peripheral nerves of diabetic mice; it can be elicited by AGEs, and prevented by a RAGE blockade. NF-kB activation was greatly reduced in RAGE-null [RAGE(−/−)] mice compared with a high increase in controls. Anesthesia (loss of pain perception), as seen in chronic diabetic neuropathy, was reversed in diabetic mice treated with sRAGE. Anesthesia was essentially prevented in RAGE(−/−) mice (Bierhaus et al. 2004).

Summary and an outlook at therapeutic interventions

In summary, we believe that glycation and AGEs play a role in neurological disorders by several mechanisms that include the toxic effects of dicarbonyls on neurons, glia and vessels, the enhancing of oxidative stress, the modification of key proteins for neuronal function, the interference with catabolism of protein aggregates and the activation of the RAGE pathway, which appears to be one of the key overarching themes and the most promising target for therapeutics. The evidence accumulated so far on the role of glycation in neurological disorders, both central and peripheral, justifies the need for further basic and translational research in this potential area.

Several agents developed for the treatment of DM complications work by suppressing either NF-κB activation itself, or the production of cytokines that stimulate NF-κB, such as TNF-α. Preliminary results in animal models are encouraging and suggest that the NF-κB pathway maybe a potential therapeutic target for diabetic vascular complications and neuropathy (Cameron and Cotter 2008). α-Lipoic acid may impair the progression or reverse peripheral diabetic neuropathy owing to its numerous antioxidant functions. Treatment with α-lipoic acid increases GSH, an important endogenous antioxidant (Deuther-Conrad et al. 2001; Vallianou et al. 2009). Therapies directed at lowering the concentrations of RAGE ligands, blocking RAGE signaling, preventing oxidative stress or lowering MGO levels could significantly decrease the development of neuropathy in DM patients (Wu and Ren 2006; Thornalley 2005; Dukic-Stefanovic et al. 2001). Further therapeutic options are carbonyl scavengers, which react with the carbonyl groups of aldose and ketose sugars and thus inactivate them before they can react with proteins. Furthermore, aminoguanidine or other hydrazine drugs, such as hydralazine, isoniazid and gentamicins, react with the carbonyl group of Amadori products. However, these agents have potential side-effects due to the depletion of essential carbonyls in the body, especially vitamin B6. Furthermore, D-penicillamine, aminoguanidine and metformin trap dicarbonyl compounds (e.g., glyoxal and MGO) to form substituted triazines (Krautwald and Münch

2010). Another dicarbonyl compound, tenilsetam, inhibits MG-induced protein cross-linking and cell death (Münch et al. 1994, 1997a; Webster et al. 2005).

Another strategy to lower MGO levels is to stimulate the anaerobic pentose phosphate pathway of glycolysis by maximizing transketolase activity by thiamine or benfotiamine supplementation, with the consequent consumption of D-glyceraldehyde-3-phosphate and increased formation of ribose-5-phosphate. Activation of transketolase may shift excess glycolytic metabolites into the pentose phosphate cycle, accelerate the glycolytic flux, and reduce intracellular free glucose, thereby preventing its conversion to MG (Thornalley 2005; Rabbani et al. 2009). Many more drugs are in the pipeline and the future clinical trials will reveal if the promising results translate into clinical application.

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