long-term diabetic complications. However, there is a paucity of evidence regarding the presence of such reciprocal interactions in peripheral nerves (Fig. **1**).

(2) AGEs and Oxidative Stress

"Glycoxidation" is a term used for the glycation processes that involve oxidative stress. In diabetes, major glycoxidation products, such as CML and pentosidine, are considered to be general markers of oxidative stress and protein damage; these products have been found to accumulate in human diabetic peripheral nerves [8,36-38]. Hyperglycemia-induced oxidative stress may be caused by a number of biochemical processes, including: glucose autoxidation and glycoxidation [39]; depletion of free radical scavengers and antioxidants [40,41]; the polyol pathway-dependent redox status [42]; overproduction of superoxide *via* the mitochondrial electron-transport chain [43]; mitochondrial fission [44]; altered polarization of the mitochondria [45]; activation of xanthine oxidase [46]; protein kinase C-dependent activation of reduced nicotinamide adenine dinucleotide (phosphate) (NAD(P)H) oxidase [47]; excessive formation of early glycation products [48] and AGEs [49]; and AGE receptor-triggering cellular oxidative stress (see below). Recent studies have demonstrated increased oxidative stress in experimental [50-54] and human diabetic neuropathy [55,56]. It has been suggested that AGEs enhance oxidative stress by reducing the level of GSH, which is the most important antioxidant in most mammalian cells [57] and, in SH-SY5Y human neuroblastoma cells, the oxidative stress in turn mediates AGE-induced cytotoxicity [58]. The AGE-induced depletion of GSH can be prevented by the radical scavengers N-acetylcysteine, alpha-lipoic acid, and 17beta-estradiol, or by the use of catalase; this indicates that superoxide and hydrogen peroxide production precedes the AGE-induced depletion of GSH [57] (Fig. **1**). Therefore, it is possible that hyperglycemia-induced oxidative stress accelerates the accumulation of AGEs, which in turn further increases the oxidative peripheral nerve injury that is associated with perturbed neuronal and Schwann cell signal transduction. In this manner, progressive fiber loss and impaired regeneration is promoted in diabetic neuropathy. Furthermore, a recent study demonstrated a concurrent increase in AGEs, neuronal nitric oxide synthase content, and oxidative stress-triggered apoptosis in pelvic ganglion neurons obtained from long-term diabetic rats. This suggests that AGEs and endogenous nitric oxide have a synergistic action in oxidative stress and irreversible nitrergic degeneration in experimental diabetic autonomic neuropathy [59].

MODIFICATION OF NEURONAL PROTEINS BY AGES AND ITS POSSIBLE IMPLICATION FOR DIABETIC NEUROPATHY

Diabetic rodent studies have shown that myelin components in both the central [60] and peripheral nerve system [61] are subject to nonenzymatic glycation. It has been suggested that AGE-modified peripheral nerve myelin is susceptible to phagocytosis by macrophages and that this stimulates macrophages to secrete protease, which may contribute to demyelination in diabetic neuropathy [62] (Fig. **2**).

Major axonal cytoskeletal proteins such as tubulin, neurofilament, and actin are also likely to undergo glycation [63-66]. These axonal proteins are central to the maintenance of axonal function and structure, and their modification by glycation may alter the structural and functional properties of the axon, thereby contributing to axonal atrophy and degeneration, as well as to slowing of axonal transport (Fig. **2**).

It has been suggested that glycation of the peripheral nerve extracellular matrix impairs peripheral nerve regeneration. The extracellular matrix protein laminin promotes the extension of neuronal processes, and glycation of a biologically active domain with laminin decreases neurite outgrowth in the murine neuroblastoma cell line [67]. More recent studies have shown similar results, in that the glycation of collagen type IV and laminin, which are major components of basal lamina, as well as of collagen type I, reduces neurite outgrowth in dorsal root ganglion neurons obtained from neonatal rats [68] and young adult mice [69] (Fig. **2**).

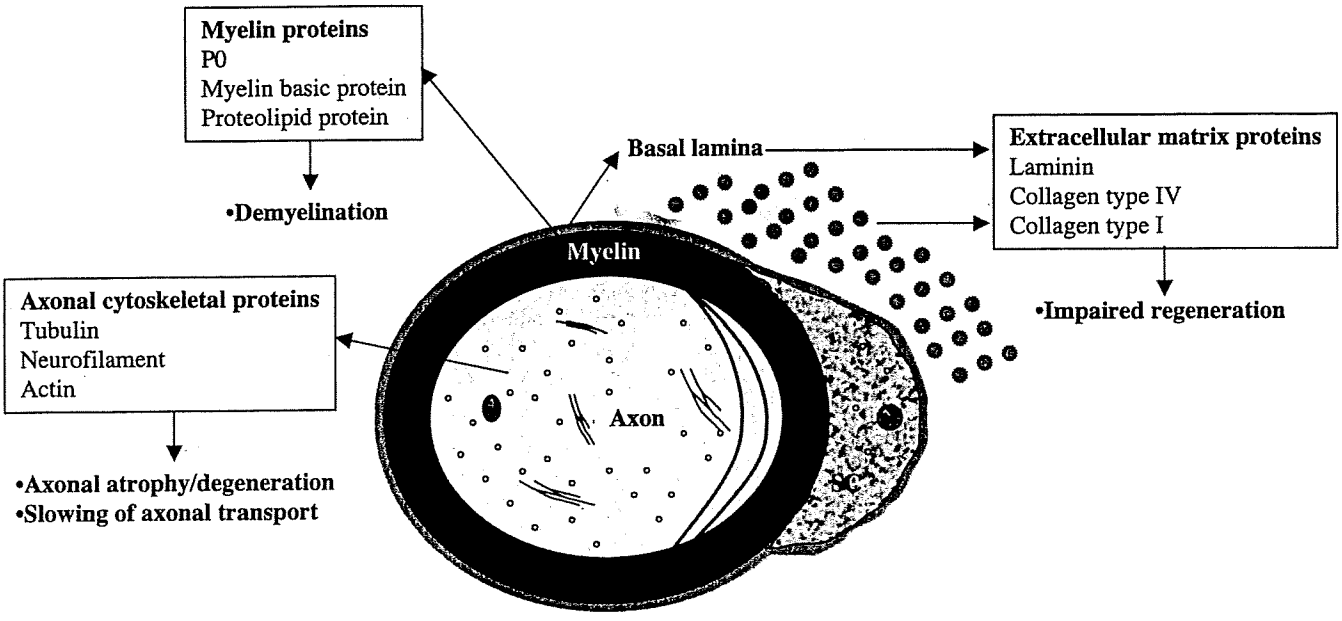

Fig. (2). Modification of neuronal proteins by AGEs and its possible implication in diabetic neuropathy.

Modification of major axonal cytoskeletal proteins and myelin components by AGEs may lead to axonal degeneration and demyelination. The extracellular matrix protein laminin may be modified by AGEs and involved in impaired regeneration in models of experimental diabetic neuropathy. However, the proposed mechanisms of AGE-induced nerve injury remain largely speculative and need to be explored in future studies. SC, Schwann cell.

ROLE FOR AGE-RAGE INTERACTION IN DIABETIC NEUROPATHY

Oxidative stress is a mediator of hyperglycemia-induced cell injury and may be promoted by the activation of intracellular signaling pathways *via* an interaction between AGEs and their receptors. RAGE is a multiligand member of the immunoglobulin superfamily of cell surface molecules with a diverse repertoire of ligands [70]; it is present in various tissues, including the peripheral nervous system [71,72]. Earlier studies reported that interaction between AGEs and RAGE results in induction of endothelial cell oxidative stress and in the activation and translocation of NF-kappaB from the cytoplasm into the nucleus [10,73], and induces vascular hyperpermeability *via* an oxidant-sensitive mechanism in diabetic vascular endothelial cells [74]. A more recent study [75] revealed that dorsal root ganglion neurons express functional RAGE and respond to the RAGE ligand with similar downstream signaling, oxidative stress, and cellular injury as occurs in other diabetic complication-prone tissues. In these neurons, activation of the RAGE-mediated signaling pathway involves formation of reactive oxygen species, caspase-3 activation, and nuclear DNA degradation; all of these are prevented by antioxidant alpha-lipoic acid treatment [75]. *In vitro* studies have shown that RAGE, through regulation of NF-kappaB expression, is an important mediator for neurite outgrowth and cell survival [76,77]. Human sural nerve biopsy studies have revealed that RAGE ligands, the receptor itself, and NF-kappaB colocalize in the perineurium, as well as in the endoneurial and epineurial vessels of patients with diabetic neuropathy [8,9] and those with impaired glucose tolerance-related peripheral neuropathy [78]; these findings suggest that activation of the AGE/RAGE/NF-kappaB signaling pathway contributes to the pathogenesis of diabetic and prediabetic neuropathy. Bierhaus *et al.* [8,10] have demonstrated that diabetes-associated loss of pain sensation and upregulation of peripheral nerve NF-kappaB and NF-kappaB–dependent proinflammatory gene expression are induced by AGE-RAGE interaction and are diminished in RAGE-null mutant mice or with the use of soluble RAGE that consists of the AGE-binding domain. A new study has reported that diabetic RAGE-null mutant mice do not develop the characteristic functional and structural abnormalities of experimental diabetic neuropathy, such as nerve conduction deficits and axonal atrophy [79] (Fig. 3).

Exposure of vascular smooth muscle cells to high glucose levels causes NF-kappaB activation and leads to oxidative stress and cellular activation *via* PKC activation[80]. In the diabetic peripheral nerve, PKC is activated in the *vasa nervorum* of diabetic rats [81] and in the vessel-rich epineurial tissue of diabetic mice [25]. Importantly, fractioned analysis of peripheral nerves has revealed that membrane PKC-alpha decreases in nerve fibers, while membrane PKC-beta increases in vascular tissues of diabetic mice overexpressing human aldose reductase, but not in vascular tissues of wild-type diabetic mice [26]. As previously described, increased polyol pathway flux contributes to generation of AGEs *via* formation of methylglyoxal and 3-deoxyglucosone, which are central precursors in the generation of an array of AGEs, including CML and pentosidine. Thus, it is possible that high glucose- and polyol pathway-mediated PKC activation and AGE accumulation, as well as AGE-RAGE interaction, occur in diabetic *vasa nervorum*. This underscores the synergistic action of the polyol pathway and the AGE/RAGE-dependent pathway in oxidative stress and NF-kappaB activation, which exaggerates neurovascular dysfunction in experimental diabetic neuropathy (Fig. 3). Furthermore, the interaction of AGEs with RAGE may lead to perturbed vascular barrier function, which is associated with an enhanced expression of vascular cell adhesion molecule-1, monocyte chemoattractant protein 1, and E-selectin [82,83]. However, it is noteworthy that there are other AGE receptors, such as the macrophage scavenger receptor and the galectin-3 receptor, that might have similar deleterious effects to RAGE when they interact with AGEs [84]. On the other hand, intracellularly generated AGEs and AGE-modified extracellular matrix lead to the generation of reactive oxygen species and thus oxidative stress *via* nonreceptor mechanisms [85].

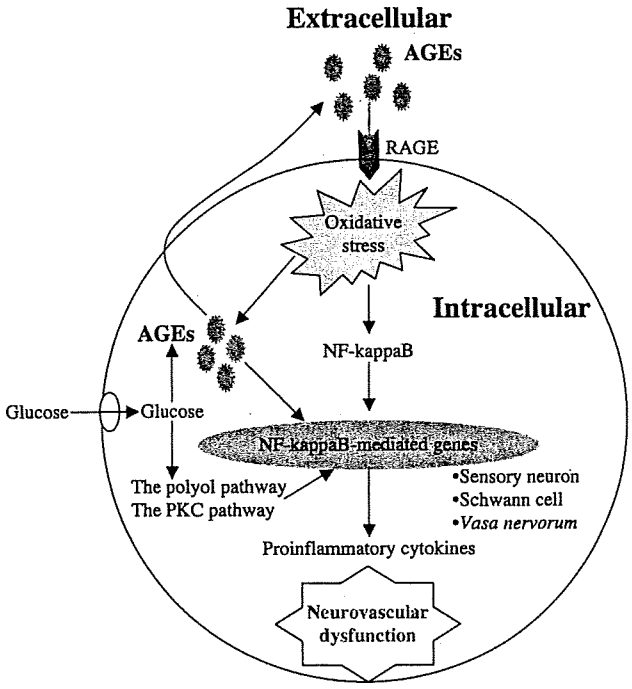

Fig. (3). Role of AGE-RAGE interaction in experimental diabetic neuropathy.

Along with increased flux through the polyol pathway and the protein kinase C pathway, AGE-RAGE-interaction induces perturbed neuronal function and structure resulting in altered pain sensation, a nerve conduction deficit, and axonal atrophy *via* upregulation of peripheral nerve nuclear factor (NF)-kappaB and NF-kappaB–dependent proinflammatory genes in diabetic animals.

AGEs, advanced glycation end products; RAGE, receptor for advanced glycation end products.

AGE ACCUMULATION IN HUMAN DIABETIC NEUROPATHY

An immunohistochemical study revealed that immunoreactivity for pyrraline, an AGE, is increased in the sclera, pia mater, cribriform plates, and connective tissues of human diabetic optic nerve[86]. Using an antiserum that specifically recognizes protein-bound CML, which is a major product of oxidative modification of glycated proteins, we [36] and other investigators [8,37] demonstrated immunolocalization of CML in perineurial basal laminae, axons, Schwann cells, and endoneurial microvessels of human peripheral nerves. The staining intensities were significantly increased in diabetic patients and were correlated with myelinated fiber loss [36]. Despite the preferential localization of CML immunoreactivity in these lesions, no direct link between the pathological changes noted in the nerve fibers and the localization of CML accumulation has been made. In this regard, perineurial cells and their basement membranes are thought to play a role in the maintenance of perifascicular diffusion barrier to the macromolecules. It is therefore possible that excessive accumulation of CML-modified adducts in the perineurium and endoneurial microvasculature alters the endoneurial microenvironment and microcirculation, thereby contributing to the development of diabetic neuropathy [36]. However, this hypothesis needs to be addressed in future studies.

A new study examined skin biopsy specimens using the immunoperoxidase technique to estimate CML and RAGE content. It was found that the perineurium of peripheral nerves and the *vasa nervorum* in the dermis were more intensely stained for CML, while stronger RAGE immunoreactivity was observed in the bundles of axons and *vasa nervorum* in type 1 diabetic patients receiving kidney transplantation alone, compared to those receiving a successful islet-after-kidney transplantation [87]. Pentosidine levels were also increased in cytoskeletal and myelin protein extracts of human sural nerves [38]. More recently, pronounced AGE immunoreactivity was detected in the axons and myelin sheaths of 90% of type 2 diabetes patients, while no AGE immunoreactivity was detected in control subjects; the intensity of the axonal AGE immunoreactivity was correlated with the severity of the structural changes that are characteristic of diabetic neuropathy, such as perineurial thickening, microvascular luminal narrowing, and axonal loss [88].

SERUM AND SKIN AGES RELATED TO SEVERITY OF HUMAN DIABETIC NEUROPATHY

Accumulation of AGEs in the skin, serum, and other specimens obtained from diabetic patients has been linked to the progression of microvascular complications, including diabetic neuropathy. Earlier studies using gas chromatography-mass spectrometry measured the levels of glycoxidation products such as CML and/or pentosidine in collagen obtained from skin-punch biopsies and demonstrated that the levels of these glycoxidation products were correlated with the severity of nephropathy, retinopathy, and vasculopathy in type 1 diabetic patients [89-91]. A more recent cross-sectional study involving 50 patients with type 2 diabetes measured AGE levels in skin, serum, saliva, and urine using spectrofluometry HPLC; the AGE levels in all specimens except for the urine increased as the patients' neuropathy, retinopathy, and nephropathy progressed [92]. Another recent study [93] measured serum CML levels using enzyme-linked immunosorbent assay with a monoclonal anti-CML antibody (6D12) in 94 type 1 diabetic children and adolescents with or without background retinopathy, microalbuminuria or neuropathy; CML levels were higher in patients with chronic complications than in patients without complications. Taking for granted the fact that CML formation depends on the oxidative condition, the increased CML levels found in the serum and tissue proteins of diabetic patients suggest that CML has a role as an endogenous biomarker of oxidative damage. Meerwaldt el al. [94] developed an AutoFluorescence Reader, a noninvasive method that uses fluorescence properties to specifically measure skin AGE contents. Using this apparatus, they assessed skin AGE accumulation in 24 diabetic patients with a history of foot ulceration, in 23 diabetic patients without clinical neuropathy, and in 21 control subjects; they found that the skin autofluorescence, which reflected tissue AGE accumulation, increased during early stages of diabetic neuropathy and was correlated with the severity of peripheral and autonomic nerve abnormalities, as well as with the presence of foot ulceration [11]. In addition, in a large group of type 2 diabetic patients, the same group confirmed that skin autofluorescence was higher in patients than in age-matched control subjects and was associated with the severity of diabetes-related complications [95]. They proposed that measurement of skin autofluorescence is a rapid and helpful tool that can be used in diabetes outpatient clinics to identify patients who are at risk for developing complications.

EFFFECTS OF ANTI-AGE AGENTS ON DIABETIC NEUROPATHY

Aminoguanidine is a highly reactive nucleophilic reagent that prevents the formation of AGEs by reacting with the carbonyl groups of reducing sugars, as well as alpha- and beta-dicarbonyl compounds such as methylglyoxal, glyoxal, and 3-deoxyglucosone. Aminoguanidine was the most promising agent for preventing AGE-mediated tissue damage caused by diabetes. In fact, initial rat studies confirmed the beneficial effect that aminoguanidine had on the development of retinopathy, nephropathy, and neuropathy. In particular, long-term aminoguanidine treatment improved the nerve conduction deficit and myelinated fiber pathology in diabetic rats [96]. Impaired nerve blood flow in diabetic rats was also normalized after aminoguanidine treatment, but such treatment had no effect on oxygen free radical activity [97]; this suggests that the hemodynamic changes were modulated without affecting oxidative stress. Short-term treatment with aminoguanidine ameliorated nerve conduction slowing and Na^+/K^+-ATPase defects, but not endothelial damage, as reflected by systemic thrombomodulin concentrations [98]. Treating diabetic rats with aminoguanidine improved endoneurial blood flow but not the impairment of endothelium-dependent vasodilation of epineurial vessels of the sciatic nerve [99,100]. The beneficial effects that aminoguanidine had on the structural alterations of endoneurial microvessels were also documented in long-term diabetic rats [101]. In contrast to these rat studies, in type 1 diabetic baboons who had diabetes for less than 5 years, treatment with aminoguanidine for 3 years did not affect impaired nerve conduction velocity, heart rate response, and myelinated fiber pathology. This suggests that, in the type 1 diabetic primate, the accumulation of AGEs is involved only in nerve damage that occurs after a more prolonged observation period [102].

A double-blinded, multiple-dose, placebo-controlled, randomized clinical trial of aminoguanidine in diabetic patients with overt diabetic nephropathy (ACTION) was completed in 1998; ACTION I involved 690 type 1 diabetic patients, and ACTION II involved 599 type 2 diabetic patients. These studies were designed to evaluate the safety and efficacy of aminoguanidine in slowing the rate of progression of renal disease in patients with overt diabetic nephropathy. The primary endpoint was doubling of the baseline serum creatinine. In ACTION I, patients received placebo, high-dose (100-600 mg per day) aminoguanidine, or low-dose (50-300 mg per day) aminoguanidine; the combined aminoguanidine dose group showed decreased progression of diabetic retinopathy and lower triglyceride, LDL cholesterol, and urinary protein levels, as well as a non-significant trend towards a slower doubling of serum creatinine. However, ACTION II was terminated prematurely due to safety concerns and apparent lack of efficacy. Reported side effects of aminoguanidine included gastrointestinal disturbance, liver function test abnormalities, flu-like symptoms, and a rare vasculitis [103]. Based on the outcomes and the side effects noted in these trials, there is no benefit in using aminoguanidine.

Other anti-AGE agents, including the thiazolidine derivative OPB-9195, have been investigated; OPB-9195 has been shown to prevent the progression of diabetic nephropathy in rats [104]. It has also been shown to improve motor nerve conduction slowing without affecting body weight and blood glucose levels in diabetic rats; the improvement was associated with reduced serum AGE levels and peripheral nerve expression of immunoreactive AGE and immunoreactive 8-hydroxy-2'-deoxyguanosine, which is a marker for oxidative stress-related DNA damage, as well as an increase in peripheral nerve (Na^+, K^+)-ATPase activity [105]. An alternative approach is to reduce tissue AGE accumulation by selectively cleaving the resultant AGE crosslinks. Diabetic rats were found to have increased mesenteric vascular AGE accumulation and mesenteric vascular hypertrophy; both of these were prevented by treatment with N-phenacylthiazolium bromide (PTB), which is a prototypic AGE crosslink breaker that attacks covalent carbon-carbon bands of dicarbonyl-derived crosslinks both *in vitro* and *in vivo* [106]. However, a more recent study has demonstrated that although AGE-breakers such as PTB and N-phenacyl-4,5-dimethylthiazolium cleave model crosslinks *in vitro*, they do not significantly cleave AGE crosslinks formed *in vivo* in skin collagen of diabetic rats [107]. Clinical trials of ALT-711, a novel AGE breaker, have shown favorable results with respect to blood pressure and vascular elasticity in aged persons with stiffened vascula-

ture [108], but treatment with ALT-711 for 2 weeks had no effects on motor nerve conduction deficit, C-fiber-mediated nociceptive dysfunction, or impaired pressure-induced vasodilation in diabetic mice after 8 weeks of diabetes [109]. Interestingly, benfotiamine, a lipophilic analogue of thiamine, is a transketolase activator that inhibits three of the four major biochemical pathways implicated in the "unifying hypothesis" of the pathogenesis of hyperglycemia-induced vascular damage: the hexosamine pathway, PKC activation, and AGE formation [110] (Fig. 1). It has higher bioavailability after oral administration and normalizes cell replication, lactate production, and AGE formation in human umbilical vein cells and bovine retinal endothelial cells cultured in high glucose concentrations [111]. In diabetic rats, the efficacy of benfotiamine with respect to peripheral nerve function and AGE accumulation has been documented, with nearly normalized nerve conduction velocity and inhibition of neural imidazole-type AGE and CML formation after 6 months of benfotiamine treatment [112]. In nondiabetic and diabetic rats, benfotiamine also reduced inflammatory and neuropathic nociception [113]. Therefore, the ability of benfotiamine to inhibit three major pathways simultaneously might be clinically useful in preventing the development and progression of diabetic complications, including neuropathy [114,115]. Finally, the formation of AGEs can also be limited by inhibitors such as pyridoxamine, tenilsetam, and 2,3-diaminophenazone, but their efficacy for treating diabetic neuropathy still remains to be explored [116].

SUMMARY

Taken together, these results indicate that accumulation of AGEs and their binding to RAGE play a key role in the pathogenesis of experimental diabetic neuropathy with increased generation of reactive oxygen species, proinflammatory cytokines, and adhesion molecules, and oxidative stress associated with activation of the NF-kappaB signaling pathway. In addition to polyol pathway hyperactivity, AGE-RAGE-mediated cellular oxidative stress further enhances the accumulation of glycoxidation products such as CML and pentosidine. Although several AGEs have been identified that accumulate in the peripheral nerve of diabetic humans and animals, in diabetic patients the accumulation of AGEs is evident in undamaged axons, Schwann cells, and *vasa nervorum* [36]. Thus, a direct linkage between AGE accumulation and nerve injury that eventually leads to progressive damage and loss of unmyelinated and myelinated nerve fibers is still lacking in the human diabetic nerve. Furthermore, no agents are in current clinical use to block AGE/RAGE signaling in diabetic patients. Therefore, further studies are needed to explore the precise mechanisms that underlie AGE-induced nerve injury and to establish the optimal therapeutic strategy for AGE/RAGE signaling blockade in human diabetic neuropathy.

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ABBREVIATIONS

AGEs	=	Advanced glycation end products
PKC	=	Protein kinase C
CML	=	N-epsilon-(carboxymethyl)lysine
RAGE	=	Receptor for AGEs
GSH	=	Reduced glutathione
MAPK	=	Mitogen-activated protein kinase
TNF	=	Tumor necrosis factor
NF-kappaB	=	Nuclear factor-kappaB
NAD(P)H	=	Reduced nicotinamide adenine dinucleotide (phosphate)
ACTION	=	Aminoguanidine in overt diabetic nephropathy
PTB	=	Phenacylthiazolium bromide

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