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The Role of Advanced Glycation Endproducts and Glyoxalase I in Diabetic Peripheral Sensory Neuropathy

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Abstract

Diabetic neuropathy is the most common and debilitating complication of diabetes mellitus with over half of all patients developing altered sensation as a result of damage to peripheral sensory neurons. Hyperglycemia results in altered nerve conduction velocities, loss of epidermal innervation, and the development of painful or painless signs and symptoms in the feet and hands. Current research has been unable to determine if a patient will develop insensate or painful neuropathy or be protected from peripheral nerve damage all together. One of the mechanisms that has been recognized to have a role in the pathogenesis of sensory neuron damage is the process of reactive dicarbonyls forming advanced glycation endproducts (AGEs) as a direct result of hyperglycemia. The glyoxalase system, composed of the enzymes glyoxalase I (GLO1) and glyoxalase II, is the main detoxification pathway involved in breaking down toxic reactive dicarbonyls before producing carbonyl stress and forming AGEs on proteins, lipids, or nucleic acids. This review discusses AGEs, GLO1, their role in diabetic neuropathy, and potential therapeutic targets of the AGE pathway.

Diabetes Mellitus

Diabetes mellitus is a chronic, multi-system metabolic disorder caused by a combination of environmental and genetic factors and characterized by hyperglycemia. The World Health Organization estimates that 220 million people worldwide currently have diabetes. Type 2 diabetes mellitus is the most prevalent form and accounts for 90-95% of these cases. According to the Center for Disease Control and Prevention, 25.8 million children and adults currently suffer from diabetes mellitus in the United States. Importantly, 35% of the adult population is estimated to have prediabetes or metabolic syndrome, a condition with higher than normal blood glucose and impaired insulin sensitivity that has yet to reach diagnostic criteria for diabetes mellitus [1]. Individuals with prediabetes are at a higher potential for developing type 2 diabetes mellitus. Hence, a staggering 79 million adults are at risk for developing type 2 diabetes mellitus. Although type 1 diabetes mellitus accounts for a far smaller percentage, 5-10% of cases, the incidence has been steadily rising in the

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past decades to nearly 5% annually in the United States [2]. Hence, both type 1 and type 2 diabetes mellitus remain growing problems throughout the world.

Despite the differences in etiology, clinical presentation, and disease prevalence, secondary complications, such as heart disease, stroke, retinopathy, nephropathy, and neuropathy, occur in both type 1 and 2 diabetes mellitus. Due to the continual rise in diabetes mellitus, secondary complications continue to be a large economic burden in the United States and across the world [3, 4]. Of these, diabetic neuropathy is the most common complication of long-term diabetes mellitus [3, 5, 6]. The Center for Disease Control and Prevention estimates 60-70% of diabetic patients will develop diabetic neuropathy symptoms with the prevalence increasing with the duration of diabetes mellitus [1]. Patients with diabetic neuropathy are at an increased risk for developing ulcers, recurrent foot infections, and Charcot joints, bony destruction and deformation due to repetitive, traumatic injury, often associated with reduced sensation in the feet [5, 7]. Consequently, diabetic neuropathy is the cause of 50-75% of non-traumatic amputations [5]. Diabetic neuropathy has a profound impact on patients' quality of life and is responsible for majority of diabetes-associated morbidity and mortality.

Diabetic neuropathy is a collection of syndromes, either focal or diffuse in nature, affecting sensory, motor, and/or autonomic peripheral neurons [5, 6]. These disorders can range from clinical to subclinical and differ in their anatomical distribution, clinical course, and spectrum of symptoms. The most prevalent of the syndromes is distal symmetrical sensorimotor polyneuropathy, referred to as diabetic neuropathy in this review, that results from damage to peripheral sensory nerves and accounts for nearly 80% of diabetic neuropathy cases [3]. One hallmark of diabetic neuropathy is the symmetrical loss of distal skin innervation due to degeneration of small cutaneous nerve fibers. Diabetes-induced nerve damage causes a dying-back of distal axons that begins in the feet and progresses proximally in a stocking-and-glove distribution [8, 9]. Diabetic peripheral neuropathy has an insidious onset and is chronic and progressive in nature; therefore, diabetic neuropathy often results in severe, irreversible symptoms after longstanding diabetes mellitus.

Sural nerve biopsies from diabetic patients also demonstrate loss of small unmyelinated C-fibers and small myelinated Aδ fibers in early stages of diabetic neuropathy with progressive involvement of large myelinated Aβ fibers with duration of disease [10, 11]. Despite histological and ultrastructural findings of axonal regeneration, collateral sprouting, and remyelination within peripheral nerves [12], impaired nerve regeneration has been documented [13, 14]. However, regeneration is ultimately unable to compensate for the continued vicious cycle of damage and neurodegeneration of sensory neurons [13, 15].

Diabetes-induced damage results in peripheral nerve pathology that correlates with clinical signs and symptoms. Nerve injury that results in structural changes can be measured through clinical neurological assessment, quantitative sensory testing, nerve conduction studies, and peripheral nerve biopsies that are often used in combination to diagnose diabetic neuropathy [16-20]. The clinical features of diabetic neuropathy can be divided based on the type of fibers that are damaged and lost. Impairment of small, myelinated Aδ fibers and unmyelinated C-fibers results in altered mechanical, thermal, and pain sensation. Deficits in vibration, proprioception, and balance are often a consequence of large, myelinated Aβ fiber damage. Sensory symptoms usually predominate in diabetic peripheral neuropathy [21], although with progression of the disease, motor dysfunction may also be present [22].

The majority of diabetic patients experience insensate neuropathy characterized by painless symptoms including reduced vibratory perception, numbness, and insensitivity to touch and pain [23, 24]. However, others have painful diabetic neuropathy that manifests as positive

symptoms of hyperalgesia, tactile allodynia, paresthesias, abnormal sensitivity to temperature, and unremitting pain [23, 25]. Data on the prevalence of painful diabetic has varied widely with some reporting a prevalence rate of 7-20% [26] and others reporting 40-50% of those with diabetic neuropathy having neuropathic complications. The European Diabetes (EURODIAB) Prospective Complications Study found approximately 25% of type 1 diabetic patients developed painful symptoms throughout the course of the 7-year investigation [26]. Although there is a considerable understanding of the molecular and pathological process responsible for damage to the peripheral nervous, the mechanisms that produce painful versus insensate signs and symptoms are not known. Furthermore, neurophysiological and histological findings do not distinguish between patients suffering with positive and negative symptoms [27]. The mechanisms underlying the development of these dichotomous symptoms remain a significant question that must be addressed to enable the development of improved and targeted therapies for diabetic neuropathy.

Hyperglycemia as a Risk Factor for Diabetic Neuropathy

A number of large studies have clearly identified hyperglycemia as a key feature involved in the pathogenesis of diabetic neuropathy [9, 28-30]. Similarly, poor glycemic control has also been recognized as an important risk factor for the development and progression of neurological complications. The Diabetes Control and Complications Trial (DCCT) followed 1,441 patients with type 1 diabetes mellitus and no history of neuropathy that were randomly assigned to either conventional therapy (one or two insulin injections daily) or intensive therapy (three or four daily insulin injections or continuous subcutaneous insulin infusion) [29]. The DCCT study found that intensive therapy reduced the risk of developing confirmed clinical neuropathy by 64% compared to conventional therapy after an average follow-up of 6.5 years [31]. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, the follow up study to the DCCT, enrolled 93% of the former intensive therapy group and 91% of former conventional therapy group to assess peripheral neuropathy for 13-14 years after the DCCT study commenced; however, due to the clear beneficial effects, the conventional treatment group was encouraged to begin and maintain intensive treatment [29]. Throughout the study period, the prevalence of clinical neuropathy and nerve conduction abnormalities continued to increase in both former treatment groups; however, the group assigned to the former intensive therapy during the DCCT study had significantly lower prevalence of indices of neuropathy despite similar glycemic control between the treatment groups [29, 32]. Similarly, the EURODIAB study found both duration of diabetes and quality of glycemic control as risk factors for the development of diabetic neuropathy [30]. Thus, prior exposure to hyperglycemia predisposed to greater risk of developing diabetic peripheral neuropathy.

Advanced Glycation Endproducts

As glucose levels rise within sensory neurons due to hyperglycemia, normal metabolic pathways become overwhelmed and excess glucose is shunted into other ancillary pathways that, under these conditions, become damaging. One consequence of hyperglycemia is the increased and accelerated production of advanced glycation endproducts (AGEs) in tissues where damage results in secondary complications, including peripheral nerves. Importantly, AGEs have been shown to have a role in the pathogenesis of diabetic neuropathy. AGEs are a heterogeneous group of molecules that form from the non-enzymatic addition of sugar moieties onto arginine and lysine residues of proteins, free amino groups on lipids, or guanine nucleic acids [33]. The process of non-enzymatic glycation was first described by L.C. Maillard in the early 1900's and even at that time, he speculated it may be an important process in diabetes [34]. It has subsequently become apparent that non-enzymatic glycation

and AGEs have a role in many disease processes such as aging, neurological disorders, and diabetic complications.

The classical AGE pathway involves the rearrangement of glucose or another reducing sugar, such as fructose, galactose, mannose, or ribose, that reacts with a free amino group of a protein, which forms a Schiff base (Figure 1) [35]. The Schiff base is highly unstable and degrades into the Amadori product or fructosamine [35]. Fructosamine is relatively stable, although levels tend to fluctuate with glucose concentrations [36]. The most well-known example of an Amadori product is hemoglobin A1c (HbA1c), a naturally occurring modification to the N-terminal valine amino group of the β chain of hemoglobin [34]. HbA1c is elevated in diabetic patients and gives an indication of glucose levels over the previous 2-3 months [37]. It is often used to monitor glucose control and has value at predicting risk of complications [9, 38]. With further rearrangement, oxidation, and elimination, fructosamine produces an AGE. Considerable progress has been made in understanding that AGEs form from specific metabolites despite the complexity of the glycation process. While intermediate steps in the glycation pathway are reversible, AGE formation is irreversible and causes modifications that result in both protease-resistant cross-linked and noncross-linked proteins [39, 40].

Besides monosaccharides, reactive dicarbonyls or α-oxoaldehydes contribute to the production of AGEs. Reactive dicarbonyls, such as 3-deoxyglucose, glyoxal, and methylglyoxal, are highly potent and reactive species that can also modify proteins, lipids, and nucleic acids and may contribute more significantly in the glycation process than the classical pathway described above (Figure 1). In fact, reactive dicarbonyls are 20,000-fold more reactive than glucose [41]. Consequently, reactive dicarbonyls have gained increasing acceptance as one of the main mechanisms that drive the production of AGEs, produce carbonyl stress, and underlie the development of diabetic complications.

Due to a combination of increased flux through glycolysis and reduced activity of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), both glyceradehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) build up in the neuron. Under normal conditions, low levels of these metabolites are converted to methylglyoxal. However, under hyperglycemic conditions, concentrations of methylglyoxal increase within the neuron due to the nonezymatic breakdown of these two glycolytic intermediates [42, 43]. Elevated levels of methylglyoxal as well as other sugars, such as fructose, lead to the formation of advanced glycation endproducts (AGEs). AGEs modify cellular components, signal through the receptor for advanced glycation endproducts (RAGE), and compromise normal neuronal function.

The longstanding view of glycation as a relatively long process that only resulted in AGE accumulation on long-lived extracellular proteins was revolutionized with the discovery of dicarbonyl metabolites [36]. Methylglyoxal and other α-oxoaldehydes form inside cells over a relatively short time period as a byproduct of many metabolic pathways [44]. Methylglyoxal is formed from spontaneous decomposition of triosephosphates, DHAP and glyceraldehyde-3-phosphate, fragmentation of other sugars, and amino acid and ketone body degradation [45-47]. Glyoxal is also a consequence of degradation of saccharides, but also of lipid peroxidation and degradation of glycated proteins [45]. Cellular concentrations of methylglyoxal and glyoxal range from 1-5 μM and 0.1-1 μM, respectively [48]. The biogenesis of 3-deoxyglucose results from the breakdown of fructose-3-phosphate from the polyol pathway [41]. It is important to note that all of these metabolic processes are enhanced in diabetes mellitus, which leads to a significant increase in the production of reactive dicarbonyls and AGEs.

Several studies have shown levels of reactive dicarbonyls are higher in patients with diabetes due to hyperglycemia [49-51]. Consequently, reactive dicarbonyl-derived AGEs are elevated in plasma and accumulate in tissues prone to secondary complications including the lens, retina, kidney, and endothelial vessels of both diabetic humans and rodents [52-56]. Indeed, the concentration of AGEs in the sciatic nerve of diabetic rats is higher than nondiabetic rodents [53, 57]. Extensive accumulation of AGEs also occurs in the skin and peripheral nerves of diabetic patients particularly in the axoplasm of myelinated and unmyelinated neurons, Schwann cells, endoneurial and epineurial microvessels, perineurial basal lamina, and perineurium, suggesting AGEs have a role in the development and/or progression of neuropathies [58-63]. A recent study investigated skin autofluorescence as a measure of AGE deposition in nondiabetic and diabetic subjects with or without neuropathy and found a correlation between slowing of sensory nerve conduction velocity (SNCV) and increased autofluorescence [64]. Similarly, levels of serum carboxymethyl lysine (CML) or skin autofluorescence were significantly higher in type 1 diabetic patients with microvascular complications, like neuropathy, compared to those without complications [65, 66].

RAGE

AGEs produce neuronal damage and dysfunction by a variety of mechanisms. AGEs interact with cell surface receptors, particularly the receptor for advanced glycation endproducts or RAGE, to induce a cascade of intracellular signaling (Figure 1). RAGE is a multi-ligand member of the immunoglobulin superfamily of cell surface receptors that signals through the phosphatidylinositol-3 kinase (PI-3K), Ki-Ras, and mitogen-activated protein kinase (MAPK) pathways [59]. RAGE is present in the DRG, peripheral nerves, Schwann cells, and epidermal fibers in rodents [67]. Transient activation of PI-3K/AKT and MAPK pathways leads to nuclear translocation of NF-κB [59, 68]. NF-κB is responsible for the expression of different classes of genes including pro-inflammatory cytokines. IL-6 and TNF-α are particularly potent cytokines that have been shown to be elevated in the sciatic nerve of diabetic mice and contribute to the pro-inflammatory state of diabetic neuropathy [69]. Continual activation of NF-κB leads to altered gene expression and upregulation of RAGE creating a positive feedback loop that enhances sensory neuron damage [70]. RAGE also stimulates NAD(P)H oxidase, a potent producer of reactive oxygen species (ROS) (Figure 1) [68]. Like glycating agents, excessive ROS alter proteins, lipids, and DNA causing damage to peripheral neurons [68].

Rodent models of diabetes mellitus have demonstrated a role for RAGE in peripheral sensory nerve damage and neuropathy symptoms. Diabetic $RAGE^{-/-}$ mice were protected from both electrophysiological and morphological deficits of the peripheral nervous system demonstrated by diabetic wildtype mice [67]. Similarly, the diabetes-induced loss of thermal pain perception and increased nociceptive thresholds were reduced in diabetic $RAGE^{-/-}$ mice [69]. Patients with diabetes also exhibit increased immunoreactivity for RAGE and AGEs in sural nerve biopsies [69], which suggests AGE-RAGE interaction may also have a role clinically in neuronal dysfunction that leads to neuropathy.

Protein Modification by AGEs

The pathophysiological consequences of AGE accumulation have been investigated in normal aging and in disease states such as Alzheimer's disease, renal failure, inflammation, and some diabetic complications [71-74]. Several mechanisms are thought to mediate AGE-damage in disease. In tissues, AGE modification of structural and cellular proteins, lipids, and nucleic acids results in dysfunction of vital cellular processes with limited proteasomal degradation, increased aggregation, and enhanced half-life of glycated proteins [35, 68].

While a number of proteins, which differ in structure and function, are known targets of the glycation process, many more likely exist that have yet to be discovered [75, 76]. However, of those proteins that have been discovered and reported, a number likely have a role in the direct dysfunction of neurons. GAPDH activity was significantly reduced following methylglyoxal treatment [77], which causes a compensatory increase of the toxic metabolite creating a pervasive, damaging cycle that leads to elevated levels of methylglyoxal and further reduction in GAPDH activity [78]. Insulin and other key insulin-signaling molecules, such as insulin receptor substrate 1, were also susceptible to dicarbonyl glycation, which may alter the neurotrophic support for sensory neurons [79, 80]. Methyglyoxal-modification of extracellular matrix reduced neurite outgrowth of sensory neurons, suggesting reactive dicarbonyls could impair the regenerative capacity of DRG neurons in diabetic neuropathy. Methylglyoxal has also been shown to alter the activity and expression of the 26S proteasome, as well as other chaperones involved with protein control [81-83]. While a number of proteins have been identified as targets for reactive dicarbonyls and explain various aspects of cellular dysfunction in diabetic neuropathy, proteins that are modified and accumulate in diabetic sensory neurons have yet to be determined.

Reactive Dicarbonyls and Mitochondrial Dysfunction

While mitochondrial dysfunction has been suggested to be one of the main pathogenic mechanisms in diabetic neuropathy, little is known about the nature and extent of mitochondrial damage resulting from chronic hyperglycemia. Mitochondria function in calcium homeostasis and a wide range of biochemical reactions, including fatty acid oxidation, nutrient production in the citric acid cycle, oxidative phosphorylation, and ATP production. Mitochondria are responsible for producing energy that cells harness for all cellular processes such as protein production, cellular transport, and cell growth and maintenance. Oxidation of NADH and $FADH_2$ from glycolysis, beta oxidation, and citric acid cycle releases electrons that are passed through a coordinated series of enzyme complexes located in the mitochondrial inner membrane and are finally transferred to oxygen. Complexes from the oxidative phosphorylation pathway use the redox energy released during electron transfer to pump protons from the mitochondrial matrix into the intermembrane space which creates an electrochemical gradient across the inner mitochondrial membrane [84]. ATP Synthase or Complex V utilizes the electrochemical gradient to produce ATP [84]. This process is particularly important for neurons given their relatively high reliance on energy production due to their increased metabolic demands [85]. Consequently, mitochondrial damage and dysfunction have been linked to common neurological disorders including diabetic neuropathy [86-88].

One mechanism by which elevated intracellular reactive dicarbonyls clearly alters mitochondrial function is through glycation of mitochondrial proteins. Multiple studies have shown that reactive dicarbonyls form AGEs on mitochondrial oxidative phosphorylation proteins and produce changes in mitochondrial respiration, activity of oxidative phosphorylation proteins, and leakage of electrons from these complexes in tissues that develop secondary complications of diabetes mellitus [73, 89-91]. However, some dispute remains if mitochondrial dysfunction results in the production of reactive oxygen species and oxidative stress in sensory neurons. A large body of evidence supporting the idea that reactive dicarbonyl damage to mitochondria results in oxidative stress comes from studies in tissues other than the peripheral nervous system [73, 89, 91-93]. While the axons of DRG neurons from diabetic rats exhibited increased ROS and oxidative stress [94], impaired respiratory function and reduced expression of certain mitochondrial oxidative phosphorylation proteins resulted in reduced production of superoxide [95, 96].

The Glyoxalase System and Protection From AGEs

The glyoxalase system, which is composed of the enzymes glyoxalase I (GLO1) and glyoxalase II (GLO2) is one mechanism that protects against AGE production. The glyoxalase system is responsible for detoxifying reactive dicarbonyls prior to the formation of an AGE (Figure 1 and 2) and was discovered independently by Dakin, Dudley, and Neuberg in 1913. At that time, its function of catalyzing the conversion of methylglyoxal to lactate was also described [35, 44]. Future studies revealed that reactive dicarbonyls, like methylglyoxal, react with reduced glutathione forming a hemithioacetal [97, 98] (Figure 2). GLO1 converts the hemithioacetal to *S*-2-hydroxyacetylglutathione. GLO2 then catalyzes this intermediate to the corresponding α-hydroxyacid and releases reduced glutathione [99].

GLO1 is considered the key enzyme in anti-glycation defense because it is the rate-limiting step in the glyoxalase pathway and prevents the accumulation of reactive dicarbonyls [100, 101]. GLO1 is highly conserved with the enzyme being described in humans, mice, yeast, plants, insects, protozoa, fungi, and many bacterial strains [99]. Due to its critical function, GLO1 has been reported to be ubiquitously expressed in the cytosol of all cells [44, 99, 102, 103]. However, we have shown Glo1 is primarily expressed at high abundance in small, unmyelinated peptidergic neurons, a subset of DRG neurons that are responsible for pain transmission in the peripheral nervous system (Figure 3) [104]. The loss of peptidergic epidermal innervation has been shown to be correlated with the development of thermal and mechanical insensitivity [105].

Since GLO1 is the major detoxification system of reactive dicarbonyls, it is plausible that differences in production and activity of the enzyme influences AGE production and the development and/or modulation of diabetic neuropathy. *Glo1* exists as a copy number variant (CNV) in many inbred strains mice where alterations in the genome that include either the gain or loss of sections of DNA result in expression differences [106, 107]. The region encompassing *GLO1* has also been reported to be a CNV in humans [108]. Studies have also recognized various SNPs and null alleles of *GLO1* in humans [109-111]. A study of patients with autism recognized the *GLO1 rs2736654* SNP results in Ala111Glu in the mature GLO1 protein and reduced activity of the enzyme [112]. Another SNP that is located in the promoter region of *GLO1* reduced promoter activity and was associated with the presence of nephropathy and retinopathy in type 2 diabetic patients [113]. These studies suggest genetic differences of *GLO1* could contribute to either the susceptibility to or protection from the development of diabetic neuropathy.

While the role GLO1 in diabetic neuropathy has received limited attention, many studies related to other secondary complications have developed a clear understanding of the protective role of GLO1 in these tissues. *In vitro* overexpression of GLO1 in endothelial cells under hyperglycemic conditions reduced reactive dicarbonyls [114] and corrected defects in angiogenesis [115] and relaxation [116]. Overexpression in the lens and retinal capillary pericytes protected against hyperglycemia-induced protein modification [117] and apoptosis [118], respectively. Similarly, markers of oxidative damage were reduced in kidneys from diabetic transgenic rats overexpressing GLO1 [90].

Our studies have utilized two inbred strains of mice that are substrains of BALB/c mice. Since these mice were separated from the same parental strain, these two substrains likely have very similar genetic backgrounds. Indeed, the substrains are isogenic at all typed SNPs [106, 119]; however, BALB/cByJ mice have a nearly 10-fold higher abundance of GLO1 in the DRG due to a known CNV. Diabetic BALB/cJ mice with reduced GLO1 levels showed increased mechanical thresholds indicative of the development of insensate neuropathy, loss of epidermal fibers, and reduced amounts of components of mitochondrial oxidative

phosphorylation proteins including Complex I and V. However, diabetic BALB/cByJ that have higher levels of GLO1 due to increased copy numbers were protected from these indices of diabetic neuropathy.

While a large proportion of patients develop altered peripheral sensation, others, nearly 30-40% of patients with diabetes, do not develop overt neuropathy signs and symptoms even after years of diabetes mellitus. A recent study highlights and complements our studies suggesting certain patients with diabetes mellitus may be protected from secondary complications due to differences in their individual genetic susceptibility. A study of Joslin Gold Medalists, patients who have survived type 1 diabetes mellitus for over 50 years, determined that current glycemic control was unrelated to the development of diabetic complications [120]. However, those patients with higher concentrations of AGEs, including methylglyoxal-derived *N*-(carboxyethyl)lysine, were 2.5 times more likely to suffer from neuropathy [120]. Those authors and others have suggested that certain patients may have an abundance of protective mechanisms that allow them to remain complication-free [121].

Therapeutic Strategies to Reduce AGEs

Therapeutic modalities can intervene at multiple levels to reduce either formation or the toxic effects of AGEs. Treatments that breakdown and/or prevent AGE crosslinking or interfere with the AGE-RAGE pathway may have benefit as clinical interventions [36]. The initial approach, however, is to reduce the formation of AGEs. Aminoguanidine, the best characterized compound, is a non-specific inhibitor of AGEs. While early clinical trials showed promising therapeutic potential [122], the ACTION II trial was terminated early due to lack of efficacy and safety concerns [123]. Despite these findings, other compounds and drugs have shown promise, both experimentally and clinically, in protecting against and/or reducing diabetic complications. Pyridoxamine showed benefit in clinical studies of diabetic nephropathy including reductions in urinary N(epsilon)-(carboxymethyl)lysine and N(epsilon)-(carboxyethyl)lysine [124]. Metformin, a common treatment for type 2 diabetes, was able to reduce levels of serum reactive dicarbonyls and AGEs in type 2 diabetic patients [125, 126]. Other compounds including aspirin, pioglitazone, benfotiamine, angiotensin converting enzyme inihbitors, angiostensin II-receptor blockers, and thiamine have also been shown to have anti-AGE effects [127]. Soluble RAGE (sRAGE) has shown promising results as a decoy receptor for AGEs by preventing the development of sensory deficits in diabetic mice with chronic administration of sRAGE [128]. A recent study using Akita mice, a spontaneous type 1 diabetic model, found fisetin, a naturally-occurring flavone, increased Glo1 expression and activity and increased the synthesis of glutathione [129]. Treatment reduced methylglyoxal modification of proteins and protected against kidney damage in these mice [129]. Investigation into other compounds like fisetin that increase GLO1 levels or activity could have profound clinical impact on reducing the incidence of diabetic complications, including diabetic neuropathy.

Conclusion

Though the pathogenesis of diabetic neuropathy involves perturbations in a number of metabolic pathways, AGEs likely play a large role in the development and/or progression of diabetic neuropathy. New research has identified neuronal populations that express enzymes to combat AGE formation, deposition, and accumulation. Genetic differences may play a key role in the vulnerability to diabetic neuropathy associated with AGE damage. Future approaches should include determination of genetic differences in humans, particularly in patients with diabetic neuropathy, which could underlie the variability in expression or activity of anti-AGE systems, like GLO1. These systems are a promising therapeutic target that could be used as an intervention in diabetic neuropathy.

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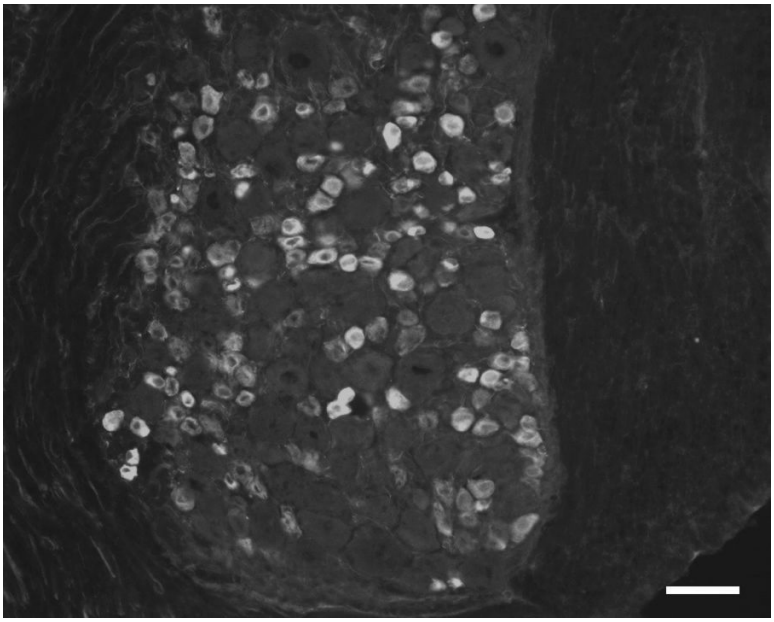

Figure 1.
A schematic illustrating the pathways that lead to the production of reactive dicarbonyls and AGEs and the mechanisms by which AGEs cause to sensory neuron dysfunction.

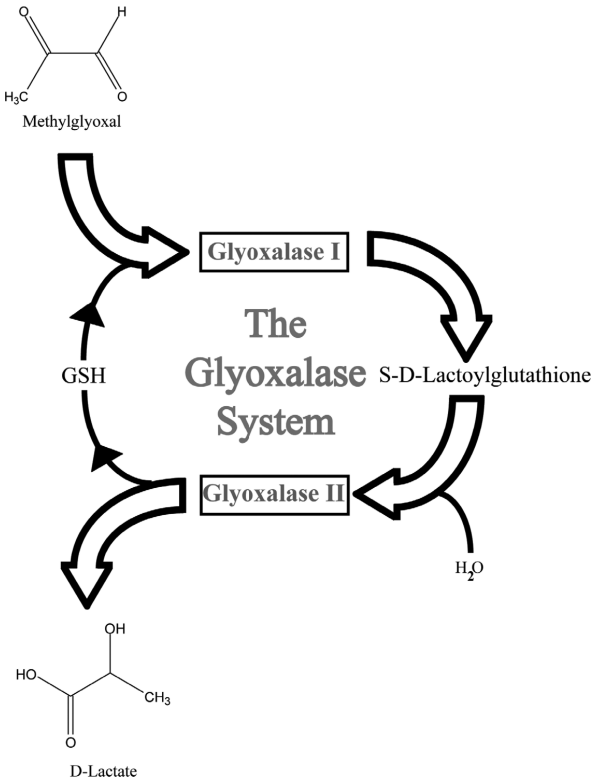

Figure 2.
The glyoxalase system is composed of two enzymes, glyoxalase I (GLO1) and glyoxalase II. Reactive dicarbonyls, like methylglyoxal, are effectively detoxified via this metabolic pathway. The glyoxalase enzyme pathway catalyzes the conversion of reactive α-oxoaldehydes into the corresponding α-hydroxyacids. In this schematic, methylglyoxal reacts with glutathione and is converted to S-D-Lactoylglutathione by GLO1. This intermediate is then broken down into D-lactate by glyoxalase II and reduced glutathione is recycled.

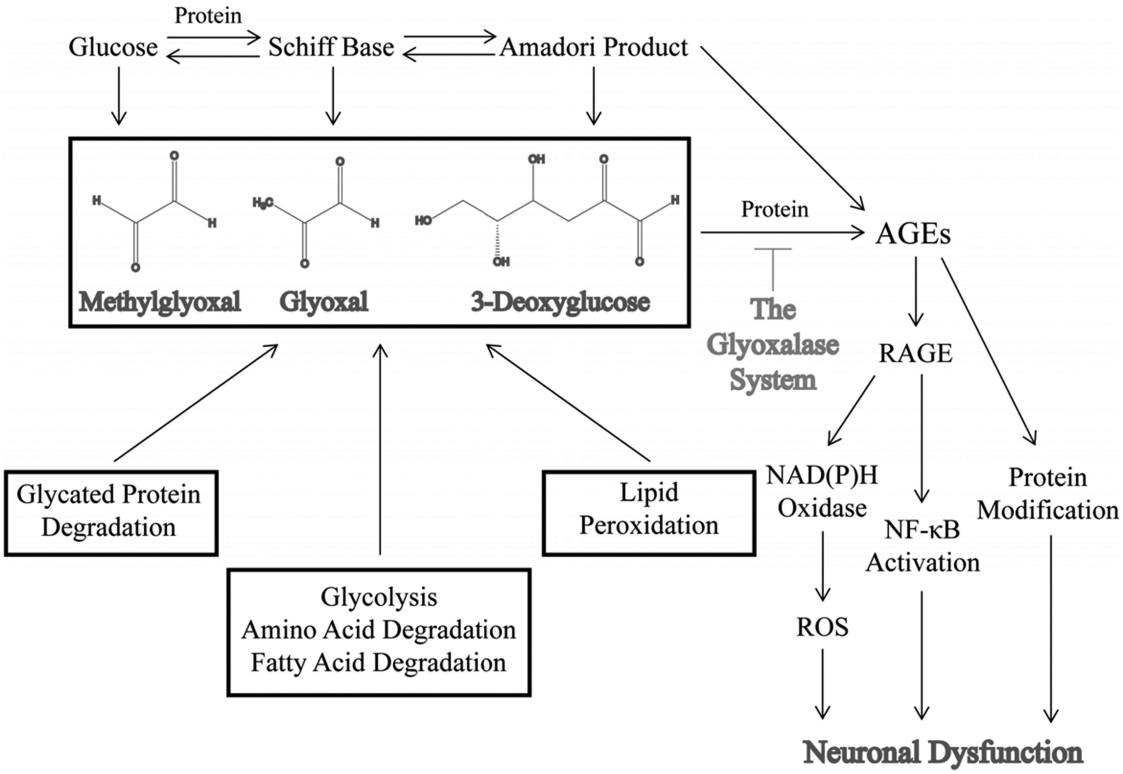

Figure 3.

The DRG from C57BL/6 mice were stained with an antibody against Glo1. Glo1 is highly abundant in small, unmyelinated peptidergic neurons. This subpopulation of neurons is particularly important in transmitting noxious pain information. Genetic differences in the expression of GLO1 in human diabetic patients may protect this neuronal population from the damaging effects of AGEs. Scale bar = 50 μm.