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Hyperlipidemia: A New Therapeutic Target for Diabetic Neuropathy

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Abstract

Emerging data establish dyslipidemia as a significant contributor to the development of diabetic neuropathy. In this review we discuss how separate metabolic imbalances, including hyperglycemia and hyperlipidemia, converge on mechanisms leading to oxidative stress in dorsal root ganglia sensory neurons. We conclude with suggestions for novel therapeutic strategies to prevent or reverse diabetes-induced nerve degeneration.

Significance of the Problem

Diabetes mellitus affects over 20 million people in the United States and the number of diabetic patients is increasing by 5% per year (www.diabetes.org). The most common complication of diabetes is diabetic neuropathy. Depending on the diagnostic criteria used, at least 50% up to 90% of individuals with diabetes will develop diabetic neuropathy. The most common form of diabetic neuropathy is diabetic polyneuropathy, a symmetric loss of nerve function beginning in the toes and progressing in a distal to proximal fashion, yielding what is commonly called a stocking/glove pattern of sensory loss (Edwards, et al., 2008). While all sensory modalities are eventually affected, recent studies show that initially small unmyelinated and thinly myelinated fibers are injured and, especially early in the disease, patients can present with pain. Twenty-five years after the diagnosis of diabetes, the cumulative risk of a lower extremity amputation is 22% and, in the general population, 60% of all lower extremity amputations are secondary to diabetic neuropathy. This represents a cost of over $22 billion per year and a significant loss of quality of life for diabetic patients (Barrett, et al., 2007). Although therapies are available to alleviate the symptoms of diabetic neuropathy, these rarely impact upon the root causes of the disease (Feldman, et al., 2002). The immense physical, psychological, and economic cost of diabetic neuropathy underscores the need for causally targeted therapies (Kles and Vinik, 2006).

Oxidative Stress in Diabetes

There is a growing consensus, driven by both clinical and basic studies, that oxidative stress underlies the development of the microvascular complications of diabetes, including diabetic

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neuropathy (Low, et al., 1997; Russell, et al., 2008; Vincent, et al., 2008; Ziegler, et al., 2004). In type 1 diabetic patients, the severity of microvascular complications parallels the degree of systemic oxidative stress (Giugliano, et al., 2008; Sullivan and Feldman, 2005). With disease and diabetic neuropathy progression, antioxidant potential decreases while lipid peroxidation products increase. Type 2 diabetic patients have a similar oxidative stress profile which directly relates to the onset and progression of microvascular complications (Greene, et al., 1999; Vincent, et al., 2004b).

In the late 1990s, our group introduced the idea that glucose-mediated oxidative stress injures the peripheral nervous system, leading to eventual death and loss of neurons and supporting Schwann cells (Feldman, et al., 1997; Russell, et al., 2001; Russell, et al., 1999; Russell, et al., 1998). Investigation of the basic mechanisms underlying this process in DRG neurons identified multiple mechanisms by which hyperglycemia mediates DRG neuron injury. Mitochondrial overload is the principal site of reactive oxygen species (ROS) generation in hyperglycemia (Vincent, et al., 2005a). DRG neurons may be preserved in vitro in the face of hyperglycemic insult by uncoupling agents that relieve the mitochondrial overload (Vincent, et al., 2004a) and by lipophilic antioxidants that protect the mitochondria against ROS injury (Vincent, et al., 2005a; Vincent, et al., 2005b).

Additional cellular mechanisms are activated by hyperglycemia to produce ROS. Hyperglycemia leads to the formation of advanced glycation end-products (AGE). DRG neurons express the receptor for AGE (RAGE) and exposure to AGE leads to oxidative stress and injury in DRG neurons that is partially mediated through activation of the nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase complex (Vincent, et al., 2007a). In addition, direct exposure to hyperglycemia leads to the activation of NAD(P)H oxidase (Vincent, et al., 2005a). This complex is formed through recruitment of a combination of a p22-phox subunit and 5 NOX subunits (Baumer, et al., 2008). Within neurons, NOX2 (or gp91-phox) and p22-phox are expressed within the cell membrane; p47-phox and p67-phox are recruited from the cytoplasm to the membrane when the neuron is exposed to a NAD(P)H oxidase activating stimulus (Murdoch, et al., 2006). NAD(P)H oxidase activity generates superoxide ($O_2^{\cdot -}$) that promotes mitochondrial dysfunction and apoptosis in the setting of inflammation, neurodegeneration and in atherosclerosis (Silver, et al., 2007; Stamler, 1996). Over time, these mechanisms act in concert with accumulating ROS-induced damage that impairs nerve function and results in the signs and symptoms of diabetic neuropathy (Feldman, et al., 1997; Feldman, et al., 2002; Greene, et al., 1999; Vincent and Feldman, 2004; Vincent, et al., 2004b; Vincent, et al., 2007b).

Pathophysiology of Diabetic Neuropathy: More than Just Glucose

Until recently, we (Feldman, et al., 1997; Feldman, et al., 2002; Greene, et al., 1999; Vincent, et al., 2004b) and other investigators (Brownlee, 2005; Low, et al., 1997; Osawa and Kato, 2005; Tomlinson and Gardiner, 2008) in the field contended that hyperglycemia was the driving force underlying the development of diabetic neuropathy. Our opinions were based originally on results from The Diabetes Control and Complications Trial (DCCT). In the DCCT, type 1 diabetic subjects receiving intensive therapy with an average glycosylated hemoglobin (HbA1c) of 7.2% had a reduced 60% cumulative incidence of diabetic

neuropathy when compared to patients receiving conventional treatment (average HbA1c of 9.0%) (The Diabetes Control and Complications Trial Research, 1993). However, the continuing longitudinal study of the DCCT, the Epidemiology of Diabetes Complications and Interventions Cohort (EDIC) yielded unanticipated results 20 years later (Genuth, 2006a; Martin, et al., 2006a; Pop-Busui, et al., 2009). Within one year of discontinuing the DCCT and beginning EDIC, the glycemic control in the two treatment groups equalized to an average HbA1c of 8% (Genuth, 2006a). All 1,300 patients were examined annually for diabetic neuropathy; one decade later patients from the intensive-DCCT cohort had a lower incidence of diabetic neuropathy compared to patients from the conventional-DCCT cohort, despite 10 years of convergent glycemic control (Martin, et al., 2006b). The underlying mechanism(s) of this result is not determined, but one interesting difference is the lipid profiles of the two groups: a subset of the intensive-DCCT cohort has less dyslipidemia than the conventional cohort (1999; Lyons, et al., 2004). This interesting, unanticipated finding is further supported by the Eurodiab Trial, a longitudinal study of over 3,000 individuals with type 1 diabetes (Tesfaye, 2007; Tesfaye, et al., 2005). Of 1,200 subjects who did not have diabetic neuropathy at baseline, hypertension, serum lipids and body mass index were each independently associated with the risk of developing diabetic neuropathy during a 7 year follow-up period. Of these risk factors, dyslipidemia was closely linked with the onset and progression of diabetic neuropathy [reviewed in (Leiter, 2005)]. In support of these findings, we recently evaluated the mechanisms underlying diabetic neuropathy progression using indexes of sural nerve morphometry obtained from two identical randomized, placebo-controlled clinical trials (Wiggin, et al., 2009a). Sural nerve myelinated fiber density, nerve conduction velocities, vibration perception thresholds, clinical symptom scores, and a visual analog scale for pain were analyzed in participants with mild to moderate diabetic neuropathy. A loss of ≥ 500 fibers/mm^2 in sural nerve myelinated fiber density over 52 weeks was defined as progressing diabetic neuropathy, and a myelinated fiber density loss of ≤ 100 fibers/mm^2 during the same time interval as nonprogressing diabetic neuropathy. In this cohort of participants elevated triglycerides was the only clinical parameter that correlated with a loss of myelinated fiber density, independent of disease duration, age, diabetes control, or other variables (Wiggin, et al., 2009a). The nerve fiber densities, triglycerides, and motor nerve conduction velocities for the two groups are presented in Fig. 1.

Dyslipidemia and Neuropathy- an Expanding Problem

The emerging idea that dyslipidemia contributes to the development of diabetic neuropathy may explain the earlier incidence of diabetic neuropathy in individuals with type 2 compared to type 1 diabetes. Lipid profiles are commonly abnormal early in the course of type 2 diabetes in a temporal pattern that correlates with the presence of diabetic neuropathy (2001; Clemens, et al., 2004). In contrast, lipid profiles are nearly always normal in type 1 patients at the time of diabetes diagnosis (Leiter, 2005). Dyslipidemia develops later in the course of type 1 diabetes, and these abnormal lipid profiles coincide with the delayed onset and progression of diabetic neuropathy (Kempler, et al., 2002; Young, et al., 1993). Accumulating data from several large scale trials of patients with type 2 diabetes also point to early dyslipidemia as a major independent risk factor for the development of diabetic

neuropathy [reviewed in (Cameron, et al., 2003; Gordon and Robinson, 2006; Leiter, 2005)]. In the United Kingdom Prospective Diabetes Study (UKPDS), 3,867 newly diagnosed type 2 patients were randomized into either intensive treatment with an oral hypoglycemic agent or insulin or conventional treatment with diet. After 10 years, intensive treatment resulted in approximately 1% lower HbA_{1c} versus conventional treatment but there was no difference in the development of diabetic neuropathy between the two groups, which had similar lipid and blood pressure profiles (1998). This finding, at first unexpected in light of the earlier DCCT data, was supported by the VA Cooperative Study, which demonstrated no difference in the prevalence of diabetic neuropathy in type 2 patients over a 2 year period comparing standard and intensive glycemic control (Azad, et al., 1999). These results suggested that independent factors other than glycemic control are critical to the development of diabetic neuropathy (Leiter, 2005).

As with EDIC and Eurodiab, analysis of the UKPDS and VA cooperative data points to dyslipidemia as a critical independent factor for the development of diabetic neuropathy (Leiter, 2005). Type 2 diabetes clusters with risk factors for coronary heart disease including obesity, hypertension, and dyslipidemia; individuals with 2 or more of these factors are diagnosed with the metabolic syndrome (Bonora, 2006; Fonseca, 2005; Grundy, 2005; Zimmet and Alberti, 2008). In a cross sectional study of 548 type 2 diabetic subjects, those with Metabolic Syndrome were twice as likely to have diabetic neuropathy (Isomaa, et al., 2001), and the driving factor was dyslipidemia. In a European study of 85 type 2 diabetic patients with at least two additional metabolic syndrome parameters, the prevalence of microvascular complications, including diabetic neuropathy, increased with each additional parameter present (Isomaa, et al., 2001); abnormalities in LDL profiles were more closely related to diabetic neuropathy than hyperglycemia. Finally, prospective studies of patients with idiopathic neuropathy, including our own recently published work, confirm a higher prevalence of hyperlipidemia than impaired glucose tolerance or hypertension, suggesting that dyslipidemia is an essential factor underlying nerve injury (Gordon and Robinson, 2006; Wiggin, et al., 2009a). Collectively, this evolving and exciting literature links dyslipidemia to the development and progression of diabetic neuropathy. Fig. 2 outlines our current understanding of the factors that contribute to the development of diabetic neuropathy.

Lipid Modification in Diabetes

We have now employed cell culture and mouse models of diabetic neuropathy and suggest oxLDLs are one notable “lipid factor” responsible for nervous system injury (Vincent, et al., 2009a). LDL is the primary carrier of cholesterol (Hammer, et al., 1995) and vitamin E (Heinecke, 1987) within the plasma. Systemic oxidative stress results in the modification of these lipoproteins, which is well characterized in atherosclerosis (Tsuzura, et al., 2004a; Willems, et al., 1998a). LDLs spontaneously oxidize in the presence of reactive oxygen species such as superoxide ($O_2^{\cdot -}$) to form oxLDLs (Hammer, et al., 1995). Cholesterol carrying LDLs are more prone to oxidation than smaller, high density particles (Krentz, 2003).

OxLDLs are critically involved in endothelial cell dysfunction, evident from the large body of literature implicating OxLDLs in atherosclerotic lesion formation (Ceriello, 2006;

Genuth, 2006b; Li and Mehta, 2005). OxLDL is strongly cytotoxic, which may explain the areas of necrosis detected within atherosclerotic lesions (Li and Mehta, 2005; Pennathur and Heinecke, 2007; Thum and Borlak, 2008; Tsuzura, et al., 2004a). In man, oxLDL is a highly analytic marker for macrovascular disease, including stroke and myocardial infarction (Tsimikas, et al., 2005). In patients with types 1 and 2 diabetes, serum levels of oxLDL in proportion to total LDL particles are associated with diabetic neuropathy (Tsuzura, et al., 2004b; Willems, et al., 1998b). Fig. 3 illustrates our findings that oxLDL increase significantly in mice on a high fat diet. These oxLDL can be found in the dorsal root ganglia and the mice develop early signs and symptoms of diabetic neuropathy (Vincent, et al., 2009a).

OxLDLs Mediate Cellular Injury via the Scavenger Receptor, LOX-1

OxLDLs cause apoptotic injury and death in both endothelial cells (Dimmeler, et al., 1997) and neurons (Draczynska-Lusiak, et al., 1998a; Draczynska-Lusiak, et al., 1998b; Keller, et al., 2000; Keller, et al., 1999; Papassotiropoulos, et al., 1996; Schroeter, et al., 2000) In endothelial cells, oxLDL induce multiple events associated with apoptotic injury, including Bid degradation, cytochrome C release, and caspase-3 activation (Vindis, et al., 2005). OxLDL are associated with increased pro-apoptotic Bax and decreased levels of the anti-apoptotic type I IGF receptor (IGF-IR) in smooth muscle cells (Higashi, et al., 2005). Both death receptor and mitochondrial pathways are involved in atherosclerotic-plaque associated apoptosis induced by oxLDL (Napoli, 2003). In neurons, oxLDL induce DNA fragmentation characteristic of apoptosis in DRG (Papassotiropoulos, et al., 1996; Vincent, et al., 2009a), striatal neurons (Draczynska-Lusiak, et al., 1998b; Schroeter, et al., 2000), and PC-12 cells (Draczynska-Lusiak, et al., 1998a). In motor neurons, oxLDL increase reactive oxygen species and activate a caspase-3-dependent death mechanism (Keller, et al., 2000). Specific effects of oxLDL on mitochondria and mitochondrial-mediated apoptotic events in neurons remain unknown.

OxLDL exert effects on cells through two primary cell surface receptors, lectin-like oxidized LDL receptor-1 (LOX-1) on endothelial cells (Chen, et al., 2006) and CD36 on macrophages (Yamashita, et al., 2006). Upon receptor-mediated uptake of oxLDL into endothelial cells, oxLDL is transported through the endothelial cell and extruded into the subendothelial region within tissues (Li and Mehta, 2005). A schematic showing the expression of LOX-1 and the potential effects of oxLDL binding is shown in Fig. 4. LOX-1 expression is upregulated by oxLDL, which in turn increases intracellular $O_2^{\cdot -}$ production (Hu, et al., 2003). Shear stress, tumor necrosis factor-α, and free radicals all increase LOX-1 expression levels (Hu, et al., 2003), while lipid lowering drugs decrease expression (Draude, et al., 1999). Hyperglycemia, advanced glycation endproducts, and C-reactive protein also increase LOX-1 expression (Iwashima, et al., 2000; Rudijanto, 2007; Schalkwijk and Stehouwer, 2005). Indeed, glucose stimulates LOX-1 expression in both endothelial cells and macrophages, prevented by antioxidants and inhibitors of MAPK and NF-κB (Dandapat, et al., 2007; Li, et al., 2003; Li, et al., 2004). LOX-1 is upregulated in renal tubules in obese, diabetic rats and its activation leads to inflammation and nephropathy (Dominguez, et al., 2008; Kelly, et al., 2008; Ueno, et al., 2003). Finally, LOX-1 is also expressed on neurons, and polymorphisms in the LOX-1 gene are associated with

neurodegenerative disease in humans (Papassotiropoulos, et al., 2005). We examined LOX-1 expression in DRG neurons, and found basal expression that was further increased by exposure to oxLDL (Vincent, et al., 2009a). Selected data are presented in Fig. 5. Subsequent to LOX-1 activation, the DRG neurons rapidly activated NAD(P)H oxidase, increased superoxide generation, and activated a programmed cell death mechanism. DRG neuron injury in the presence of oxLDL was prevented by a LOX-1 blocking antibody, the NAD(P)H oxidase inhibitor apocyanin, or the antioxidant α-lipoic acid (Vincent, et al., 2009a).

These data suggest that, in diabetes, neurons are exposed to both glucose and oxLDL which independently increase ROS, and glucose may sensitize neurons to oxLDL-mediated damage via upregulation of LOX-1. Interestingly, oxLDL decreases native LDL-receptor expression in a LOX-1-dependent manner (Hu, et al., 2003). Given the critical role for native LDL-receptors in neuronal functioning, synapse maintenance, and myelination following injury (Herz and Bock, 2002), oxLDL could also predispose neurons to glucose-mediated injury by decreasing native LDL-receptor. These ideas await further exploration.

Lipids and Diabetic Neuropathy

If the idea that dyslipidemia contributes to the development of diabetic neuropathy is true (McManis, et al., 1994), lipid lowering drugs may be beneficial in the treatment of diabetic neuropathy. Fenofibrate is a PPARα agonist that lowers plasma lipids by improving their removal by the liver and improving fatty acid metabolism (Aasum, et al., 2008; Harano, et al., 2006). In genetic dyslipidemia in mice, including ApoE knockout, leptin deficient, and LDL receptor knockout mice, fenofibrate improves the lipid profile and increases HDL (Kooistra, et al., 2006; Lie, et al., 2005; Srivastava, et al., 2006). These lipid improvements correlate with prevention of insulin resistance and atherosclerosis (Aasum, et al., 2008; Calkin, et al., 2007; Xie, et al., 2007). Interest in this drug treatment has expanded with the demonstration that fenofibrate dramatically improves hyperglycemia, insulin resistance, albuminuria, and glomerular lesions in db/db mice (Park, et al., 2006). The FIELD trial demonstrated that fenofibrate improves signs and progression of retinopathy and nephropathy (2007; Davis, et al., 2008; Firth, 2008; Keech, et al., 2007; Simo and Hernandez, 2007). The Fremantle Diabetes Study was an observational investigation of 1,237 patients with type 2 diabetes. The data suggest that therapy with a statin or fibrate protects against diabetic peripheral sensory neuropathy, but calls for confirmatory evidence via a randomized clinical trial (Davis, et al., 2008). Fenofibrate also may provide neuroprotection against stroke (Deplanque, et al., 2003). We recently demonstrated potent ability of fenofibrate to prevent hyperglycemia-induced DRG neuron injury in vitro by decreasing mitochondrial $O_2^{\cdot -}$ generation (Vincent and Feldman, 2008). We are following this study with an intervention in type 1 diabetic mice and have demonstrated that 0.1% w/w fenofibrate chow significantly decreases total cholesterol and LDL triglycerides (unpublished data).

Future Directions

We maintain our stand that hyperglycemia also is a key mediator of DRG neuron injury particularly in poorly-controlled diabetes. Therefore, compounds that improve glycemic control will assist in the prevention of complications. Metformin, a biguanide compound, improves insulin resistance by reducing gluconeogenesis and enhancing peripheral glucose uptake, promoting reduction of the plasma glucose level (Yoon, et al., 2007). Metformin remains one of the most used glucose regulating drugs in type 2 diabetes (Saenz, et al., 2005) and is used in preclinical trials in mice (Algire, et al., 2008; Yoon, et al., 2007). Interestingly, dyslipidemia increases in adolescent type 1 diabetic patients with poor glycemic control, again highlighting the complex interplay between glycemia and dyslipidemia (Shamir, et al., 2008). Taken together, the data indicate that strategic use of NAD(P)H oxidase inhibition, antioxidants, anti-LOX-1 therapy, anti-hyperglycemia, and lipid lowering therapies will prevent diabetic neuropathy. Each of these components has been tested in rodents with positive results (Cotter and Cameron, 2003; Dominguez, et al., 2008; Park, et al., 2006). Individually, these strategies have not produced significant results in clinical trials, with the exception of α-lipoic acid (Ziegler, et al., 2006). Current investigations are focusing in on metabolic deficits in the axon, particularly at the mitochondria (Edwards, et al., 2009; Figueroa-Romero, et al., 2008; Wiggin, et al., 2008). Further drug refinement and subcellular targeting may be the key to improved efficacy against neuronal injury.

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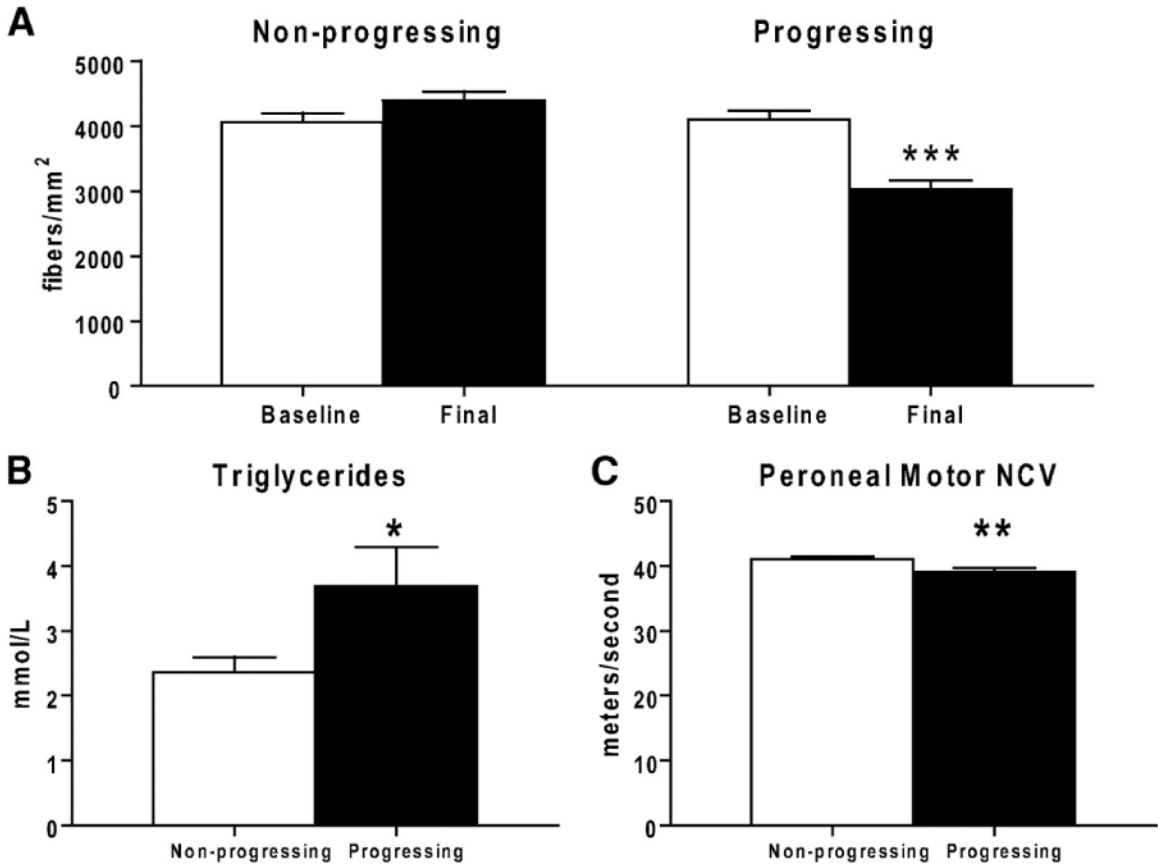


Fig. 1. Myelinated fiber density (MFD) of the rapidly progressing and nonprogressing diabetic patients

(A): The nonprogressing dataset shows a no change in MFD (fibers/mm2) over 52 weeks, while the progressing dataset shows a highly significant decrease in MFD. Baseline measurements of triglyceride levels (B) and peroneal motor nerve conduction velocity (C) are significantly different between the progressing and nonprogressing participants. *P < 0.05; ** P < 0.01; *** P < 0.0001. (reproduced from (Wiggin, et al., 2009b)).

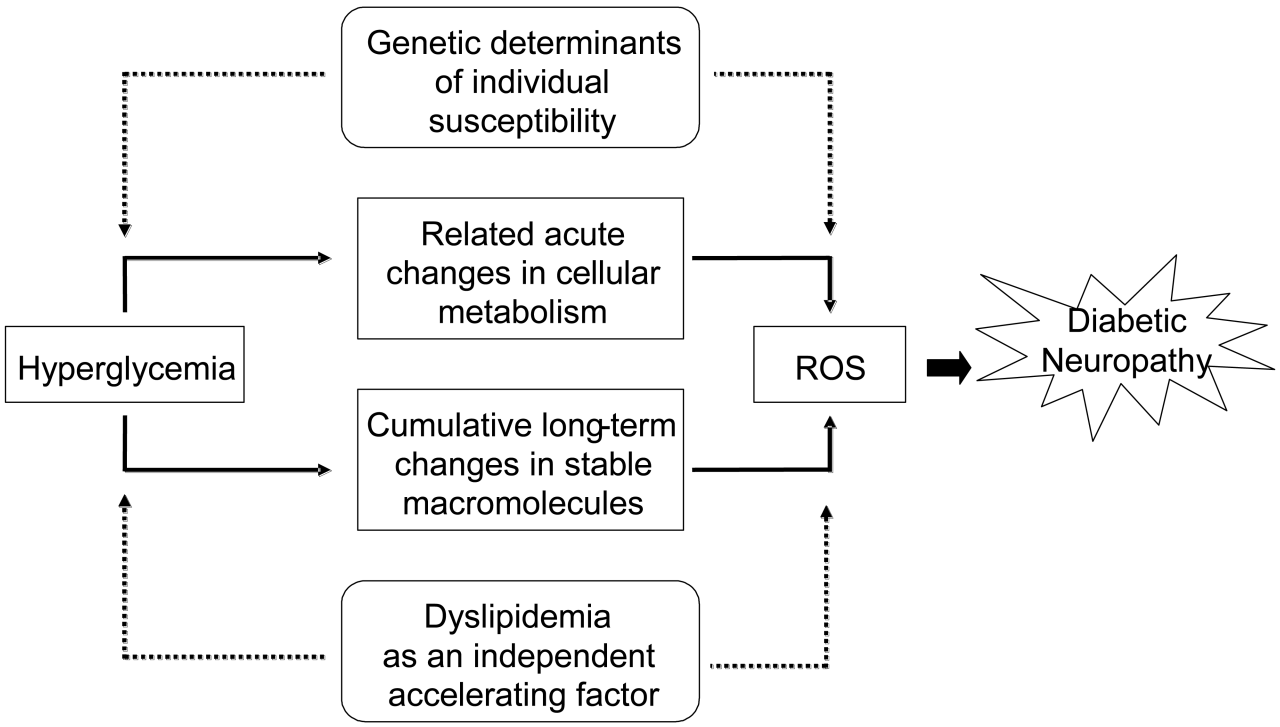
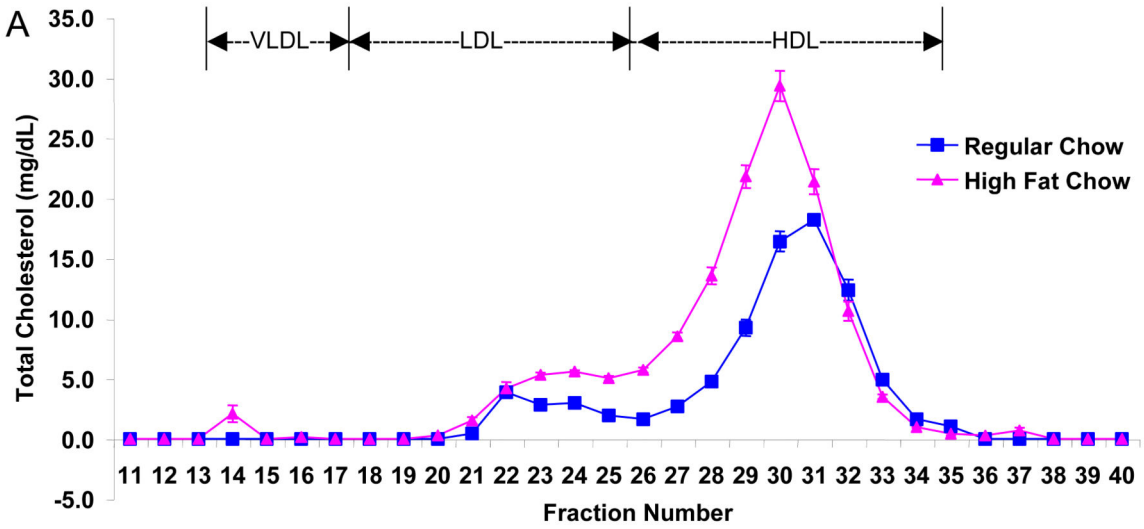
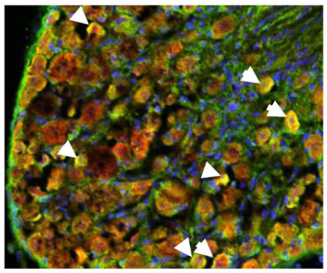


Fig. 2. Hyperglycemia and hyperlipidemia contribute to the pathogenesis of diabetic neuropathy
Adapted from (Brownlee, 2005).



B

LDL Oxidation	Control	High Fat
HODE (pmol/mg protein)	116+14	193+10
Dityrosine (μmol/mol tyrosine)	23+2	546+91
Nitrotyrosine	90+11	144+57



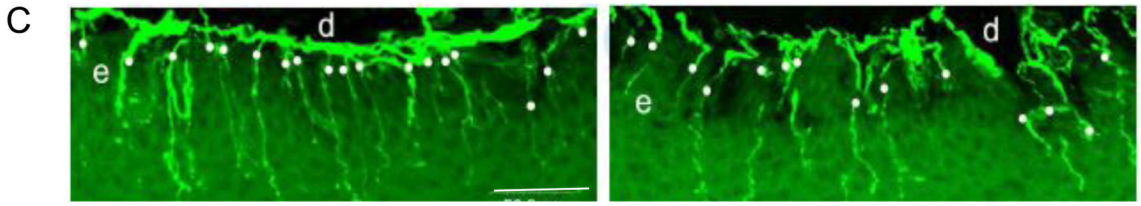


Fig. 3. Mice on a High Fat Diet Increase oxLDL and Develop Neuropathy

(A) Pooled plasma samples (2 pools/group, each pool analyzed 3 times) were subjected to fractionation by FPLC, then cholesterol (A) were measured in each fraction. The graph shows the mean and SEM for n=2 pools/group. (B) Oxidative stress measures in the LDL fraction by reverse phase HPLC. HODE, dityrosine, and nitrotyrosine were all significantly increased ($p<0.05$). (C) Representative IENFD images from one control and one high fat fed mouse footpad. Bar = 50 μm; d=dermis, e=epidermis. White dots indicate nerve fibers counted. (D) In a different mouse study, using obese db/db mice, we immunostained the DRG for ApoB and MDA-oxidized LDL. We observe co-localization of MDA-LDL in green and ApoB in red (yielding a yellow signal) around the neurons (arrows). (A-C reproduced from (Vincent, et al., 2009b)).

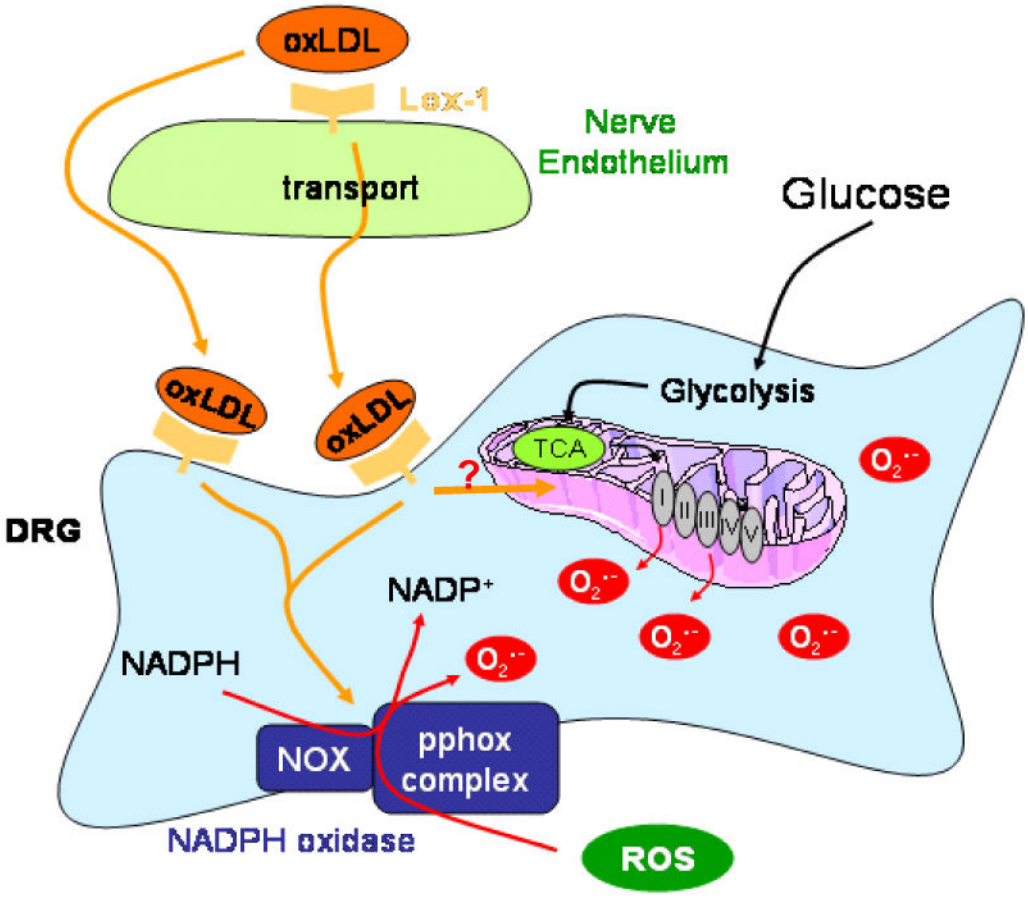


Fig. 4. Schematic of Effects of oxLDL Binding to LOX-1

LOX-1 on both vascular endothelial cells and DRG neurons will bind oxLDL. Subsequently, the oxLDL may be endocytosed or transcytosed. Receptor binding initiates a signaling pathway leading to the activation of NAD(P)H oxidase and also may alter mitochondrial generation of reactive oxygen species. Glucose independently affects these same cellular targets.

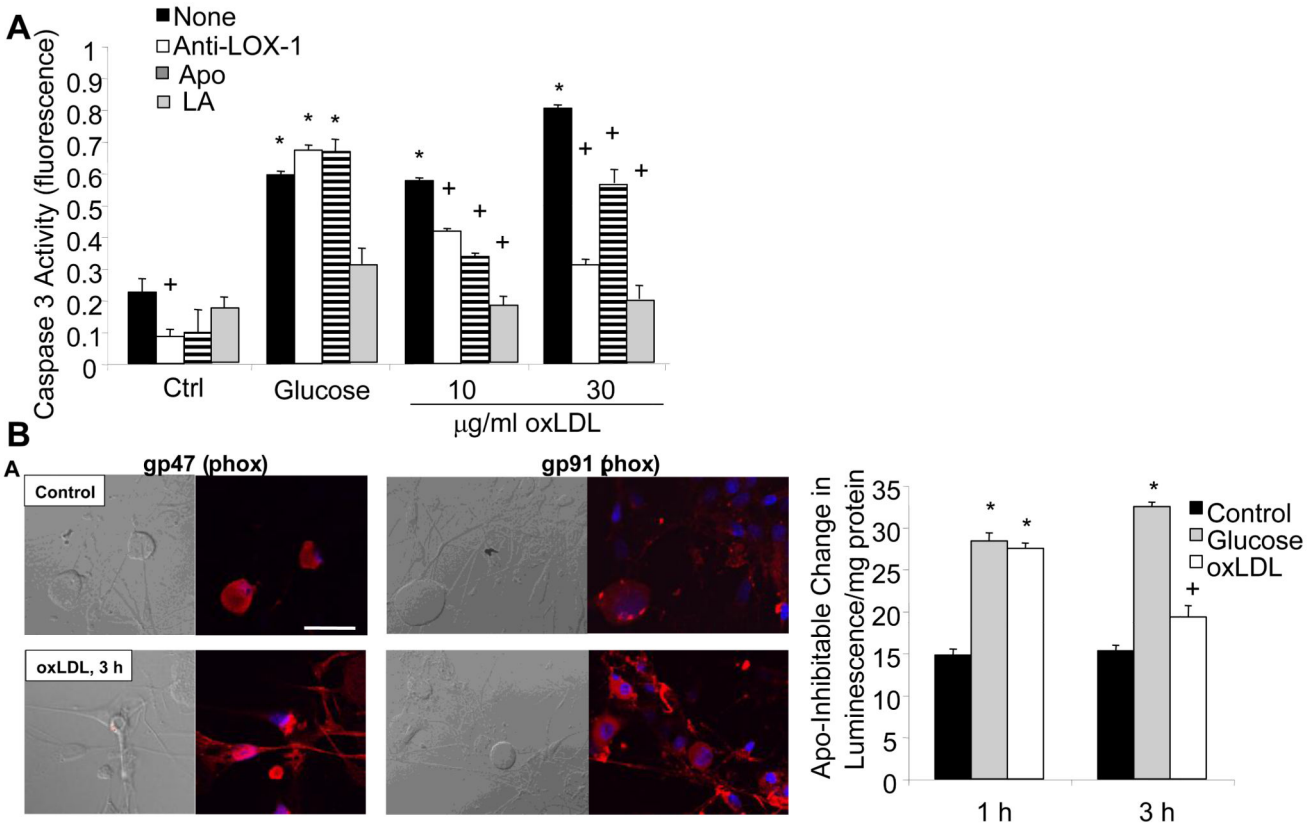


Fig. 5. High glucose and oxLDL cause cell death in DRG neurons via NAD(P)H Oxidase

Adult DRG neurons were exposed to high glucose (25.7 mM) or increasing concentrations of oxLDL and then cell death was quantitated by caspase 3 activation after 5 h. DRG neurons were additionally pre-treated with LOX-1 neutralizing antibody (Anti-LOX-1, 100 mg/ml), apocyanin (Apo, 1 μM), or α-lipoic acid (LA, 100 μM). n=9, *p<0.01 compared to untreated control, +p<0.01 compared to no pre-treatment (None). (B) Adult DRG neurons were exposed to 30 μg/ml oxLDL and then immunolabeled for NAD(P)H oxidase subunits p47 or gp91. In (B), adult DRG neurons were exposed to high glucose (25.7 mM) or oxLDL (30 μg/ml) for 1 h or 3 h, then lysed for biochemical assays of NAD(P)H oxidase. *p<0.01 compared to untreated control, +p<0.05 compared to untreated control. (reproduced from (Vincent, et al., 2009b)).