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Commentary

Chewing the fat: Genetic approaches to model dyslipidemia-induced diabetic neuropathy in mice

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ABSTRACT

Emerging clinical evidence now suggests that dyslipidemia may be strongly linked with the development and progression of neuropathy in diabetic patients, and dyslipidemia is considered an important risk factor for the development of diabetic neuropathy. However, because of important species differences, current animal models fall short of accurately replicating human diabetic dyslipidemia. Rodents resist expansion in low-density lipoprotein cholesterol (LDL-C) and typically maintain or increase high-density lipoprotein cholesterol (HDL-C), despite prolonged high-fat feeding. Here, we discuss the findings of Hinder et al., in which they utilized novel genetic experimental approaches to develop a diabetic mouse model with human-like dyslipidemia. The authors created a mouse with an apolipoprotein E (ApoE) knockout in conjunction with a leptin receptor mutation. A triple mutant mouse with both ApoE and apolipoprotein B48 knockout and leptin deficiency was also created in an effort to generate a model of diabetic dyslipidemia that better mimics the human condition. The long-term goal of these studies is to develop more faithful models to address how hyperglycemia and hyperlipidemia may drive the development and progression of neuropathy. Hinder and colleagues were successful at creating a diabetic mouse model with severe hypertriglyceridemia, hypercholesterolemia, and a significant increase in the total cholesterol to HDL-C ratio. This work was successful in establishing a model of diabetic dyslipidemia that more closely emulates the poor lipid profile observed in human diabetic patients with neuropathy. This commentary will also review current models used to study the effects of dyslipidemia on diabetic neuropathy and highlight a proposed mechanism for the role of dyslipidemia in the pathogenesis of diabetic neuropathy.

Dyslipidemia is an independent risk factor for diabetic neuropathy

The majority of diabetic patients will develop diabetic neuropathy, which is the most common and debilitating complication of diabetes (Rutkove, 2009; Vincent et al., 2009b; Zochodne, 2008). Hyperglycemia plays a key role in the development and progression of diabetic neuropathy (Edwards et al., 2008; Feldman, 2008; Figueroa-Romero et al., 2008; Sinnreich et al., 2005; Sumner et al., 2003), and a combination of multiple etiologies, each stemming from the initial insult of hyperglycemia, is likely responsible for the dying-back type axonal degeneration that underlies neuropathic symptoms (Edwards et al., 2008; Feldman, 2008; Figueroa-Romero et al., 2008). In light of long withstanding evidence that hyperglycemia is the leading cause of diabetic neuropathy (Anon., 1988, 1993, 1999; Feldman et al., 1997; Franklin et al., 1990; Greene et al., 1999), evidence from several large clinical studies indicates that metabolic derangements such as a poor lipid profile are linked with neuropathy development and progression, independent of glycemic control (Leiter, 2005; Lyons et al., 2004; Tesfaye, 2007; Tesfaye et al., 2005; Wiggin et al., 2009). Consequently, dyslipidemia has recently been identified as a major independent risk factor for the development of neuropathy [reviewed in (Vincent et al., 2009b)].

Poor lipid profiles correlate with the onset of symptoms of type 2 diabetic patients (Clemens et al., 2004). In addition, elevated triglycerides correlate with the progression of diabetic neuropathy independent of disease duration, age, glycemic control, or body mass index (BMI) (Wiggin et al., 2009). Furthermore, nondiabetic patients with idiopathic neuropathy with and without impaired glucose tolerance had a significantly higher rate of dyslipidemia compared to diabetic patients without neuropathy (Smith et al., 2008). Despite the growing body of clinical literature which suggests that diabetic patients with a poor lipid profile are at increased risk for developing neuropathy, few rodent models of diabetic neuropathy have incorporated dyslipidemia.

Cellular mechanisms of dyslipidemia in diabetic neuropathy

Although the association of dyslipidemia and neuropathy has been identified in clinical studies, the mechanisms by which lipids damage sensory neurons and contribute to pathogenesis of diabetic neuropathy are unclear. It is possible that increased high-density lipoproteins

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(HDLs), despite an otherwise poor lipid profile, may reduce peripheral lipid deposits and interfere with the influence of other lipoproteins on sensory neurons in diabetic patients. Vincent et al. (2009b) proposed a mechanism suggesting that elevated low-density lipoproteins (LDLs) have increased susceptibility to oxidation and oxidized LDLs (oxLDLs) induce cellular effects that lead to neuronal injury in the dorsal root ganglia (DRG) by binding the oxLDL receptor (LOX-1) receptor expressed on DRG neurons in a similar manner to oxLDL binding to its receptor in vascular endothelial cells (Chen et al., 2007) and renal tubular cells (Kelly et al., 2008). Vincent et al. also reported that oxLDLs are increased in the plasma of mice fed a high-fat diet and confirmed that the LOX-1 receptor is expressed on DRG neurons. Exposure of cultured rat DRG neurons to oxLDLs also increased LOX-1 expression and dose dependently increased oxidative stress via LOX-1 (Vincent et al., 2009a). In addition, these studies suggested that oxLDL is involved with LOX-1 induced neuron injury primarily by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation that results in increased superoxide production (Vincent et al., 2009a). Fig. 1, adapted from Vincent et al. (2009a) highlights this novel mechanism for dyslipidemia-induced sensory neuron damage in which oxLDL binding to LOX-1 induces NADPH oxidase activation and results in superoxide generation in DRG neurons. Because activation of LOX-1 on endothelial cells has also been reported to induce oxidative stress and inflammation (Li et al., 2004; Mehta et al., 2004), it is plausible to suggest that oxLDLs could doubly contribute to neuropathy via both vascular and neuronal injury.

Demyelination resulting from lipid dysregulation is another potential mechanism of lipid induced neuronal injury. Segmental demyelination is a key feature in human patients with diabetic neuropathy, and myelin breakdown with focal demyelination has been shown to occur in high-fat-fed rodents (Xie et al., 2013). Thus, it is plausible to suggest that genetically or high-fat diet induced dyslipidemia may negatively impact myelination status in peripheral nerves and contribute to sensorimotor deficits.

Dyslipidemic animal models of diabetic neuropathy

To date, few studies have evaluated neuropathy and the lipid profile in rodents (Coppey et al., 2012; Guilford et al., 2011; Kumar et al., 2009; Obrosova et al., 2007; Vincent et al., 2009a) and most of these studies have been performed in high-fat-fed rodents. Although high-fat-fed mice develop neuropathy-like symptoms, including sensory and motor nerve conduction velocity deficits, reduced epidermal innervation, mechanical allodynia, thermal hypoalgesia, and mild hyperlipidemia (Guilford et al., 2011; Vincent et al., 2009a), the current dyslipidemic models fail to acquire all facets of the poor lipid profile observed in human dyslipidemia.

Human diabetic patients with dyslipidemia typically exhibit increased triglycerides, elevated LDL-C and reduced HDL-C. In mice, Vincent et al. reported a 100% increase in HDL that was accompanied by increased cholesterol uptake by HDL in high-fat fed mice compared to mice fed a control diet (Vincent et al., 2009a). Even though high-fat

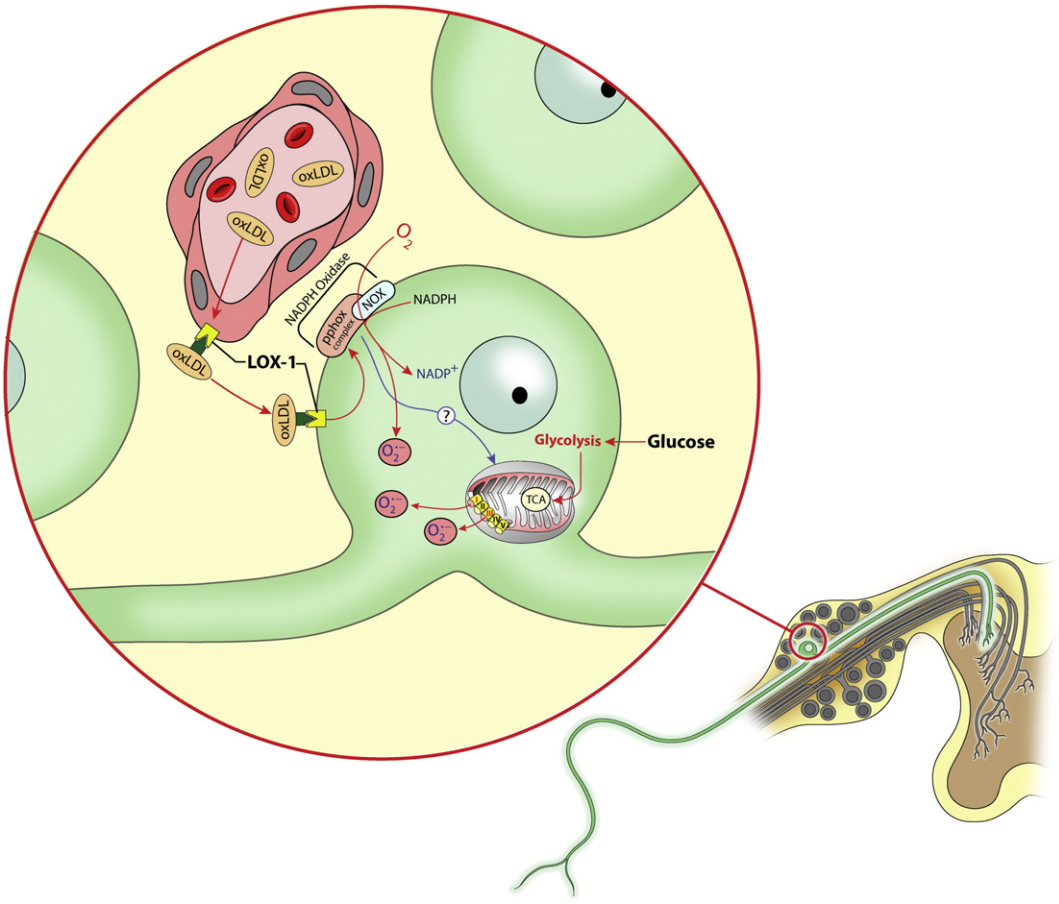

Fig. 1. Putative mechanisms for dyslipidemia-induced sensory neuron injury. Schematic diagram illustrating the DRG, with an enlarged inset of a DRG neuron and adjacent blood vessel. The oxidized form of LDL (oxLDL) binds to the LOX-1 receptor in vascular endothelial cells and DRG neurons and is subsequently endocytosed or transcytosed. oxLDL is thought to activate NADPH oxidase via interactions with the LOX-1 receptor, resulting in non-mitochondrial superoxide generation. In addition, NADPH oxidase may increase mitochondrial production of reactive oxygen species. Finally, glucose may independently induce mitochondrial superoxide production and increase endothelial LOX-1 expression. This schematic illustration was adapted from Vincent et al. (2009b) with permission from John Wiley and Sons, Ltd.