Mouse Models of Diabetic Neuropathy

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Abstract

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes and is associated with significant morbidity and mortality. DPN is characterized by progressive, distal-to-proximal degeneration of peripheral nerves that leads to pain, weakness, and eventual loss of sensation. The mechanisms underlying DPN pathogenesis are uncertain, and other than tight glycemic control in type 1 patients, there is no effective treatment. Mouse models of type 1 (T1DM) and type 2 diabetes (T2DM) are critical to improving our understanding of DPN pathophysiology and developing novel treatment strategies. In this review, we discuss the most widely used T1DM and T2DM mouse models for DPN research, with emphasis on the main neurologic phenotype of each model. We also discuss important considerations for selecting appropriate models for T1DM and T2DM DPN studies and describe the promise of novel emerging diabetic mouse models for DPN research. The development, characterization, and comprehensive neurologic phenotyping of clinically relevant mouse models for T1DM and T2DM will provide valuable resources for future studies examining DPN pathogenesis and novel therapeutic strategies.

Key Words: diabetic peripheral neuropathy; diet-induced obesity; leptin; mouse models; nerve fiber density; nerve conduction velocity; type 1 diabetes; type 2 diabetes

Introduction

Diabetes is a metabolic disorder characterized by high blood glucose. Approximately 95% of diabetes is type 2 diabetes mellitus (T2DM), or non-insulin-dependent diabetes mellitus, resulting from an insensitivity or resistance to insulin (CDC 2011). The remaining 5% of cases consist of type 1 diabetes mellitus (T1DM), or insulin-dependent diabetes mellitus, attributed to a loss of insulin production and signaling (CDC 2011). Diabetes has reached epidemic proportions worldwide. Recent statistics from the International Diabetes Federation indicate that more than 371 million people have diabetes and that the number of cases is increasing in every country (International Diabetes Federation 2012). In China alone, more than 90 million people have been diagnosed with diabetes (Yang et al. 2010), representing roughly a quarter of the global diabetic population. To further compound the scale of the global epidemic, the economic cost of diabetes is staggering. The American Diabetes Association reported that the total 2012 estimated cost of direct medical expenditures attributed to diabetes in the United States was $176 billion, with another $69 billion in indirect costs due to work absenteeism and reduced workplace productivity (Eizirik et al. 2013).

The micro- and macrovascular complications of diabetes are potentially devastating and affect multiple organs and tissues, including the eyes, kidney, heart, and nerves. Approximately 60% of all diabetic patients develop diabetic peripheral neuropathy (DPN), the most common microvascular complication (CDC 2011; Vincent et al. 2011). DPN is characterized by a progressive distal-to-proximal degeneration of peripheral nerves, which results in sensory symptoms, including pain, weakness, and/or loss of sensation. DPN is associated with significant morbidity and mortality, and other than tight glycemic control, no effective treatments are available. Because DPN pathophysiology is not completely understood, determining the underlying mechanisms that cause nerve injury and prevent nerve regeneration is of paramount importance for the development of successful therapeutic interventions.

In vivo models are critical for understanding DPN pathophysiology and elucidating treatment strategies, and the increasing prevalence of diabetes worldwide has fueled the development of a number of diabetic mouse models. Several established diabetic mouse models exhibit neurological impairments associated with DPN, and new diabetic mouse strains that are more physiologically relevant to the human disease continue to be explored. This review will discuss the most widely used mouse models of DPN, including the main phenotypic characteristics of each model, how to choose the appropriate model, and important considerations when working with selected strains. Furthermore, we discuss the
Diabetic Peripheral Neuropathy

To maximize translational research potential, investigators must select a model of DPN that mimics the key physiologic and metabolic conditions found in humans. This section summarizes the clinical and pathologic features of DPN in patients and discusses the available guidelines and methods for assessing these features in mice.

Clinical Presentation of DPN

DPN is characterized by length-dependent loss of sensation that adopts a “stocking-glove” pattern, where the longest axons to the feet are affected first, followed by the hands. Loss of sensation progresses in a distal-to-proximal fashion. Clinical manifestations, including numbness, tingling, pain, or weakness, differ depending on which nerve fibers are involved. Large diameter myelinated Aβ fibers are associated with cutaneous mechanoreceptors, and the large diameter thinly myelinated Aδ fibers and unmyelinated small diameter C fibers transduce temperature and pain (Chen et al. 2005). Neuropathy involving the smaller nerve fibers appears first and is characterized by hyperalgesia and allodynia (an increased sensitivity to painful or nonpainful stimuli, respectively) (Callaghan, Cheng, et al. 2012). Progression then involves dysfunction and degeneration of larger myelinated nerve fibers, resulting in a loss of ankle reflexes, sensory ataxia, and decreased proprioception (Tesfaye et al. 2010). Patients ultimately develop hypoalgesia and completely lose sensation (Callaghan, Cheng, et al. 2012). DPN is a major cause of diabetes-related morbidity: the initial pain hypersensitivity can be disabling, and the ensuing insensitivity combined with poor wound healing can compound minor lesions on the feet. In extreme, but not uncommon circumstances, nontraumatic lower limb amputation may be necessary to remove diseased tissue that arises from ulcer formation and infection. The prognosis for amputees is quite poor, with more than 30% risk of death within one year of surgery due to severe disability and associated comorbidities (Dillingham et al. 2005).

DPN Etiology

Although the precise etiology of DPN remains largely unclear, the growing consensus is that DPN results from the impact of metabolic and physiologic imbalances within the nerve environment, with the effects of diabetes impacting the nerve directly as well as the microvasculature supplying the nerves. Chronic hyperglycemia and elevated levels of plasma glucose produce metabolic abnormalities and contribute to nerve damage by triggering dysfunctional biochemical mechanisms (Vincent et al. 2011), including the generation of advanced glycation end products (Jack and Wright 2012), increased activity of the polyol pathway (Oates 2002), and protein kinase C activity (Geraldes and King 2010). Inflammation (Wilson and Wright 2011), impaired insulin signaling (Kim and Feldman 2012), mitochondrial reactive oxygen species production (Hinder et al. 2012), endoplasmic reticulum stress (Lupachyk, Watcho, Obrosov, et al. 2013; Lupachyk, Watcho, Stavniichuk et al. 2013), and dyslipidemia (Vincent, Hayes, et al. 2009; Wiggins et al. 2009) have also been linked to abnormal cellular homeostasis and DPN progression. Vascular disease is also present in diabetes, with microvascular pathophysiology contributing to DPN in both humans and experimental models of diabetes (Tesfaye et al. 1994). As DPN progresses, neuronal dysfunction closely coincides with the development of endoneurial microangiopathy (Britland et al. 1990; Malik et al. 1992; Yasuda and Dyck 1987), capillary basement membrane thickening (Fagerberg 1959), and endothelial hyperplasia (Timperley et al. 1976). These vascular abnormalities promote diminished oxygen tension and hypoxia, resulting in neuronal ischemia.

Further confounding our understanding of DPN pathogenic mechanisms is the recent suggestion that DPN in T1DM and T2DM may be inherently separate disorders (Callaghan, Hur, and Feldman 2012). This premise is based on results from a number of clinical trials examining the efficacy of strict glucose control on DPN prevalence. Whereas maintaining glucose control attenuated DPN onset and progression in T1DM populations, no similar beneficial correlations have been observed in T2DM populations, suggesting that there are fundamental differences in DPN etiology in T1DM and T2DM (Callaghan, Hur, and Feldman 2012). The impact of hyperglycemia and other factors associated with metabolic diseases that must be considered when selecting appropriate DPN mouse models will be discussed further in later sections of this review.

Guidelines for Assessing DPN in Mice

Mouse models provide an important tool for study of the pathogenesis, prevention, and treatment of diabetic complications, including DPN. They are relatively low in cost and require simple husbandry, and the ease of genetic manipulation permits targeted research. In response to the diabetes epidemic and consequent surge in diabetes research, the National Institutes of Health formed the Diabetic Complications Consortium (DiaComp; www.diacomp.org last accessed 10/08/2013), formerly the Animal Models of Diabetic Complications Consortium. The primary goal of DiaComp is to identify and characterize novel animal models of diabetic complications. DiaComp also provides a central resource for phenotyping protocols and established criteria to define and characterize diabetic complications as a means to minimize inter-investigator variability and maximize the impact of new studies.

DPN diagnosis in patients involves testing for the presence of abnormal sensory symptoms, nerve conduction...
velocity (NCV) deficits, and decreases in myelinated fiber and/or intraepidermal nerve fiber densities (IENFDs). Similarly, characterization of DPN in mice uses a set of routine phenotyping methods to assess behavioral responses, NCVs, and anatomical features, as recommended and recognized by DiaComp. Sensory function is determined by assessing allodynia, hyperalgesia, and hypoalgesia through behavioral responses to thermal or mechanical stimuli. The tail-flick and hindpaw withdrawal tests are recommended by DiaComp for assessing thermal sensitivity, and Von Frey filaments are an alternative approach to assess tactile responses of the hindpaw (Chaplan et al. 1994). Thermal hypersensitivity and tactile allodynia are common early in the course of DPN, whereas decreased responses and hyposensitivity occur later (Chaplan et al. 1994). DiaComp also recommends measuring motor and sensory NCVs to assess nerve function because these measures represent the gold standard approach to identify electrophysiologic neuronal deficits, and IENFD and/or myelinated fiber density assessments are performed to examine neurological morphology on an anatomical level. IENFD is a sensitive marker of small sensory nerve fiber loss in both clinical and experimental studies (Kellogg et al. 2007; Pittenger et al. 2004; Quattrini et al. 2007; Sullivan et al. 2007). In certain instances, DPN can also be further characterized using immunohistochemistry to examine oxidative and nitrosative stress, inflammatory infiltrates, and impaired angiogenesis within peripheral nerve tissue (Dauch et al. 2013; Kusano et al. 2004; Schratzberger et al. 2001; Vareniuk et al. 2007).

To fully characterize DPN in mouse models, the metabolic phenotype must also be determined. Body weights, fasting blood glucose, and impaired glucose tolerance (IGT) are measured longitudinally. In mice, the onset of diabetes is typically defined when fasting hyperglycemia levels surpass 150 mg/dL (Sullivan et al. 2007). In addition to hyperglycemia, dyslipidemia is also associated with T2DM (Vincent, Hayes, et al. 2009; Vincent, Hinder, et al. 2009); therefore, characterization of lipid profiles is important when studying aspects of dyslipidemia that correlate to nerve injury. Comprehensive metabolic measurements include recording glycolated hemoglobin and plasma insulin, lipid analysis of plasma cholesterol and triglycerides, and fast protein liquid chromatography analysis to determine the ratios of cholesterol and triglycerides to lipoproteins.

Further details on the guidelines for phenotyping DPN in mice are provided elsewhere (Sullivan et al. 2008). Overall, the most useful mouse models for DPN should exhibit sensory deficits, electrophysiologic measures of nerve impairment, and anatomic evidence of nerve fiber loss (Apfel et al. 2001) that follow the typical course of DPN onset and progression in humans, as summarized in Figure 1.

**T1DM Mouse Models**

T1DM accounts for approximately 5% of the diabetic population and typically presents in childhood or adolescence (CDC 2011). T1DM is characterized by the progressive autoimmune destruction of insulin-producing pancreatic β cells resulting in insulinopenia and systemic hyperglycemia. Patients are dependent on exogenous insulin therapy to control their diabetes.

To aid in the investigation of T1DM pathogenesis, a number of T1DM animal models are available, such as chemically-induced streptozotocin (STZ)-based models and spontaneous mouse models of T1DM. These models accurately mimic the metabolic phenotype of T1DM and develop DPN; however, these models do not reflect the severity of human DPN and display only mild neurophysiologic deficits (Beiswenger et al. 2008; Li et al. 2005; Sullivan et al. 2007; Wright and Nukada 1994). An overview of these models, including available DPN phenotype data, is discussed below and summarized in Table 1.

**Streptozotocin-Induced Diabetes in Mice**

Pancreatic β cell ablation by STZ is the most common approach to induce T1DM. The popularity of this model stems from the ease of diabetes induction and the ability to consistently synchronize diabetes in a cohort of animals. STZ is a nitrosourea analogue with structural similarities to glucose that preferentially accumulates in insulin-producing β cells by glucose transporter 2 (Leiter 1982; Wilson and Leiter 1990). The high toxicity of STZ is attributed to its powerful alkylating activity that interferes with glucose transport (Wang and Gleichmann 1998) and induces DNA double-strand breaks (Bolzan and Bianchi 2002). Hyperglycemia from STZ administration is induced using one of two paradigms recommended by DiaComp: a single high dose (SHD; approximately 150 mg/kg) or consecutive multiple low doses (MLDs; approximately 50 mg/kg/day for 5 days) of STZ.

Although both approaches induce diabetes and mice develop a neuropathic phenotype (Sullivan et al. 2008), there are critical differences resulting from these diabetes induction approaches that warrant consideration when designing DPN experimental studies. The SHD-STZ model exhibits a robust and early neuropathic phenotype, and changes in neuropathic function, including increased thermal latency, decreased mechanical sensitivity, decreased NCV, and decreased IENFD, are typically observed by 12 weeks after STZ administration (Demiot et al. 2006; Jack et al. 2012; Johnson et al. 2008; Lupachyk, Watcho, Stavniuchuk et al. 2013; Muller et al. 2008; Obrosova et al. 2005). However, the SHD-STZ model is associated with severe toxicity and high levels of postinjection mortality (Ventura-Sobrevilla et al. 2011).

The MLD-STZ approach is less toxic, with a slowly progressive β cell death, gradual elevation of blood glucose levels, and subsequent lymphocytic infiltration of pancreatic islets, which more closely resembles events that occur in human pathology (McEvoy et al. 1984). However, the MLD-STZ model exhibits moderate to no neuropathy...
phenotype, depending on the strain. C57BL/6 mice are the most commonly used model of MLD-STZ and display elevated fasting blood glucose and glycated hemoglobin levels 2 to 3 weeks after injection (Leiter 1982; Ventura-Sobrevilla et al. 2011). Although one study indicated that these mice exhibit increased thermal latency, decreased mechanical sensitivity, and decreased motor and sensory NCVs by 24 weeks after induction (Korngut et al. 2012), other studies have shown no significant deficits in neurologic function, despite sustained hyperglycemia (Sullivan et al. 2007; Vincent et al. 2007). C57BL/6 mice, when crossed with 129S7 or 129/Sv mice, however, do exhibit significant NCV deficits (Kellogg and Pop-Busui 2005; Kellogg et al. 2007; Li et al. 2004). Swiss Wistar mice display significantly decreased motor NCVs, diminished nerve action potentials, axon atrophy, and myelin thinning 6 to 9 months after MLD-STZ (Kennedy and Zochodne 2005).

Spontaneous and Genetic Models of T1DM

Selective inbreeding has produced several spontaneous T1DM mouse models, including nonobese diabetic (NOD) and B6Ins2^Akita^ mice. NOD mice develop diabetes as a consequence of a heritable polygenic immunodeficiency that closely resembles T1DM in humans (Leiter 2001). Mediated by CD4- and CD8-positive T cell autoimmune responses against pancreatic β cells, insulinitis typically develops

Figure 1 Typical presentation of common diabetic peripheral neuropathy (DPN) features. Neuropathy in patients typically presents with mild-to-moderate pain and hypersensitivity that may progress to severe pain sensations. Peripheral axon dysfunction eventually leads to sensory loss, loss of ankle reflexes, and decreased proprioception. Potential late complications include ulcerations and the need for nontraumatic amputations. In mouse models of DPN, tactile allostynia and thermal hyperalgesia are assessed using Von Frey filaments, hindpaw withdrawal, or tail-flick tests. These behavioral assays are also used to detect the onset of mechanical and thermal hypoalgesia. At this point in DPN progression, electrophysiological evidence of sensory nerve dysfunction (sensory NCV) and intraepidermal nerve fiber (IENFD) loss are also present. Finally, large myelinated nerve fiber dysfunction is reflected in electrophysiological motor NCV assays and in altered sural nerve myelinated fiber density (MFD).
<table>
<thead>
<tr>
<th>Strain</th>
<th>STZ Dose, mg/kg</th>
<th>Diabetes duration, weeks after STZ</th>
<th>Neuropathy phenotype*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single high dose STZ</strong></td>
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<tr>
<td>BALB/cJ</td>
<td>260</td>
<td>6</td>
<td>Tactile hypoalgesia (5 wks)</td>
<td>Jack et al. 2012</td>
</tr>
<tr>
<td>Swiss Mice</td>
<td>200</td>
<td>8</td>
<td>Thermal hypoalgesia</td>
<td>Demiot et al. 2006</td>
</tr>
<tr>
<td>MrgD</td>
<td>180</td>
<td>8</td>
<td>Thermal hypoalgesia (4 wks)</td>
<td>Johnson et al. 2008</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>150</td>
<td>8</td>
<td>Tactile hypoalgesia (4 wks)</td>
<td>Obrosova et al. 2005</td>
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<td></td>
<td>180</td>
<td>10</td>
<td>—</td>
<td>Muller et al. 2008</td>
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<td>100°</td>
<td>12</td>
<td>—</td>
<td>Thermal hypoalgesia</td>
<td>Lupachyk, Watcho, Stavniichuk et al. 2013</td>
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<tr>
<td><strong>Multiple low dose STZ</strong></td>
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<tr>
<td>129S7</td>
<td>40 (×5)</td>
<td>24</td>
<td>—</td>
<td>Kellogg and Pop-Busui 2005</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>40 (×5)</td>
<td>24</td>
<td>—</td>
<td>Kellogg et al. 2007</td>
</tr>
<tr>
<td>ICR</td>
<td>45 (×5)</td>
<td>~8</td>
<td>Thermal hypoalgesia</td>
<td>Homs et al. 2011</td>
</tr>
<tr>
<td>NOD</td>
<td>35 (×5)</td>
<td>~8</td>
<td>Thermal hypoalgesia</td>
<td>Homs et al. 2011</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>40 (×5)</td>
<td>12</td>
<td>Thermal hypoalgesia</td>
<td>Tam et al. 2004</td>
</tr>
<tr>
<td></td>
<td>50 (×5)</td>
<td>24</td>
<td>Absence of thermal analgesia</td>
<td>Sullivan et al. 2007</td>
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<tr>
<td></td>
<td>55, 70, 85</td>
<td>24</td>
<td>Thermal hypoalgesia</td>
<td>Vincent et al. 2007</td>
</tr>
<tr>
<td></td>
<td>50 (×5)</td>
<td>24</td>
<td>Absence of thermal analgesia</td>
<td>Sullivan et al. 2007</td>
</tr>
<tr>
<td>DBA/2J</td>
<td>40 (×5)</td>
<td>24</td>
<td>Thermal hypoalgesia</td>
<td>Wiggin et al. 2008</td>
</tr>
<tr>
<td>Swiss Webster</td>
<td>85, 70, 55</td>
<td>22, 26</td>
<td>↑ Thermal latency</td>
<td>Kan et al. 2012</td>
</tr>
<tr>
<td></td>
<td>60, 50, 40</td>
<td>32</td>
<td>↓ Mechanical sensitivity</td>
<td>Toth et al. 2008</td>
</tr>
<tr>
<td>Swiss Wistar</td>
<td>85, 70, 55</td>
<td>36</td>
<td>—</td>
<td>Kennedy and Zochodne 2005</td>
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</table>

Continued
around 4 weeks of age, and frank diabetes onset ensues around 12 to 14 weeks of age (Delovitch and Singh 1997; Ize-Ludlow et al. 2011; Leiter 2001). Given the polygenic basis of spontaneous T1DM in NOD mice, however, this progression is susceptible to variability, and factors such as housing status and diet can affect diabetes development and the prevalence of diabetes within cohorts (Leiter 2001). Sex also affects diabetes onset in NOD mice, and female mice are used more frequently because they develop T1DM symptoms earlier and at a higher frequency than male mice (Leiter 2001). This unpredictability of diabetes onset confers the need for a high number of mice to have a meaningfully sized cohort with similar diabetic phenotypes. Thus, relatively little neuropathy characterization has been performed in these mice, but studies demonstrate the presence of hyperalgesia as early as 8 weeks of age and hypoalgesia at 12 weeks of age (Gabra and Sirois 2005; Obrosova et al. 2005).

B6Ins2Akita mice develop spontaneous T1DM because of a point mutation in the \textit{Ins2} insulin gene that results in impaired insulin secretion and subsequent hyperglycemia (Yoshioka et al. 1997). Notably, these mice retain their ability to respond to exogenous insulin (Schmidt et al. 2011). B6Ins2Akita mice are on the C57BL/6 background and demonstrate diabetes onset at 7 weeks of age and decreased sensory NCV as early as 16 weeks of age (Choeiri et al. 2005). However, despite their robust diabetic phenotype, no significant impairments in sensory or motor NCVs at 24 weeks of age were observed in a subsequent study, although trends of increased tail-flick latency and significant hindpaw hyperalgesia were observed (Sullivan et al. 2007). These data suggest that DPN progression may be more gradual in this model and that further neurological characterization is required.

**T2DM Mouse Models**

T2DM is the most prevalent form of diabetes and accounts for approximately 95% of diabetic cases (CDC 2011). It is generally held that T2DM is the result of a combination of factors, including genetic background, the Western diet, and sedentary lifestyle. These factors culminate in insulin resistance and often present as IGT and prediabetes before the onset of overt hyperglycemia and diabetes. Furthermore, T2DM is a component of the metabolic syndrome; therefore, features of the metabolic syndrome, including obesity, cholesterol, high blood pressure, and triglycerides, may also contribute to DPN pathogenesis in T2DM.

Numerous T2DM mouse models are available and can be classified as (1) genetic, (2) spontaneous, or (3) diet-induced models. The neuropathic phenotype in T2DM mice, however, has been characterized in only a few strains. Similar to T1DM models, there is strain-dependent variability in neuropathy phenotype, and it does not always correlate with degree and duration of hyperglycemia (Brussee et al. 2008; Sullivan et al. 2007). Similarly, because sex-based differences on diet-induced diabetes exist in certain mouse strains (Leiter 1989; www.jax.org last accessed 10/08/2013),

<table>
<thead>
<tr>
<th>Strain</th>
<th>STZ Dose, mg/kg</th>
<th>Diabetes duration, weeks after STZ</th>
<th>STZ Age, wks</th>
<th>Spontaneous STZ Neuropathy phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOD</td>
<td>18</td>
<td>32</td>
<td>28</td>
<td>Thermal hypoalgesia (8 wks)</td>
<td>Obrosova et al. 2005</td>
</tr>
<tr>
<td>Akita</td>
<td>28</td>
<td>20</td>
<td>20</td>
<td>Thermal hypoalgesia (16 wks)</td>
<td>Gabra and Sirois 2005</td>
</tr>
<tr>
<td>B6Ins2Akita</td>
<td>28</td>
<td>16</td>
<td>16</td>
<td>Thermal hypoalgesia (16 wks)</td>
<td>Elias et al. 1998</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>Thermal hypoalgesia (16 wks)</td>
<td>Choeiri et al. 2005</td>
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<td></td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>Absence of thermal analgesia, Ns Δ SNCV, Δ MNCV</td>
<td>Sullivan et al. 2007</td>
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<td></td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>Thermal hypoalgesia (16 wks)</td>
<td>Kakoki et al. 2010</td>
</tr>
</tbody>
</table>

**Table 1**

- **STZ**: streptozotocin
- **Dose**: mg/kg
- **Diabetes duration, weeks after STZ**: number of weeks after STZ
- **STZ Age, wks**: age of STZ treatment
- **Spontaneous STZ Neuropathy phenotype**: thermal hypoalgesia
- **Reference**: source of information
also indicate the sex of mice used for these studies, although no direct sex-based comparisons have been noted regarding DPN to our knowledge at this time. An overview of T2DM mouse models, including available DPN phenotype data, is discussed below and summarized in Tables 2 and 3.

Genetic T2DM Mouse Models

Monogenic mouse models with impaired leptin signaling are prevalent in DPN research (Table 2) because mice carrying these mutations typically develop significant nerve deficits. Leptin is a hormone that is secreted postprandially from adipocytes and controls appetite by hypothalamic signaling. Genetic mutations in leptin (ob/ob mice) or its receptor (db/db mice) result in compromised leptin signaling and a diabetic metabolic profile brought on by hyperphagia and consequent obesity, hyperglycemia, and hyperinsulinemia. C57BKS db/db mice, one of the first mouse models of DPN (Sima and Robertson 1978), typically develop diabetes at 4 weeks of age, exhibit hyperalgesia and allodynia between 8 and 12 weeks of age, and exhibit hypoalgesia after 12 weeks of age (Cheng et al. 2009; Li et al. 2005; Kan et al. 2012; Sullivan et al. 2007; Wang et al. 2011). Profound deficits in motor and sensory NCV are also present, as are structural abnormalities typically indicative of DPN (Cheng et al. 2009; Li et al. 2005; Kan et al. 2012; Sullivan et al. 2007; Wang et al. 2011). Importantly, some inconsistencies have been noted relating to the phenotype of db/db mice on this background. Although certain studies have demonstrated abnormal responses to thermal and mechanical stimuli (Dauch et al. 2012; Li et al. 2005; Sullivan et al. 2007; Wang et al. 2011), another demonstrated the presence of tactile allodynia but no significant thermal hypoalgesia or IENFD changes.

Table 2 Leptin-Based Mouse Models of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Strain</th>
<th>Age, wks</th>
<th>Neuropathy phenotype</th>
<th>NCV</th>
<th>Anatomy</th>
<th>Reference</th>
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<tbody>
<tr>
<td>C57BKS db/db</td>
<td>12–16</td>
<td>Thermal hypoalgesia</td>
<td>↓ MNCV (8–12 wks)</td>
<td>—</td>
<td>Li et al. 2005</td>
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<tr>
<td></td>
<td>24</td>
<td>Thermal hypoalgesia</td>
<td>↓ MNCV (16 wks)</td>
<td>↓ SNCV (16 wks)</td>
<td>Wang et al. 2011</td>
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<td></td>
<td></td>
<td>Tactile hypoalgesia</td>
<td>↓ MNCV (16 wks)</td>
<td>↓ IENFD</td>
<td>Cheng et al. 2009</td>
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<td></td>
<td>21</td>
<td>Tactile allodynia</td>
<td>—</td>
<td>—</td>
<td>Wright et al. 2007</td>
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<td></td>
<td>16</td>
<td>Tactile hypoalgesia</td>
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<td>Ns △ IENFD</td>
<td>Wright et al. 2007</td>
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<td></td>
<td>18</td>
<td>Absence of thermal</td>
<td>↓ MNCV (14 wks)</td>
<td>↓ IENFD</td>
<td>Kan et al. 2012</td>
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<td>analgesia</td>
<td>↓ SNCV (14 wks)</td>
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<td>Tactile hypoalgesia</td>
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<td>Sullivan et al. 2007</td>
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<td></td>
<td>24</td>
<td>Thermal analgesia</td>
<td>↓ MNCV</td>
<td>↓ IENFD</td>
<td>Sullivan et al. 2007</td>
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<td></td>
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<td>↓ SNCV</td>
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<td></td>
<td>32</td>
<td>Mechanical hyperalgesia</td>
<td>MNCV</td>
<td>Neuronal loss evident in DRG</td>
<td>Shi et al. 2013</td>
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<td>(10 wks)</td>
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<td>Cold allodynia</td>
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<td>(10 wks)</td>
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<td>Tactile hypoalgesia</td>
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<td></td>
<td></td>
<td>(18 wks)</td>
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<tr>
<td>C57BL/6 db/db</td>
<td>24</td>
<td>Thermal hypoalgesia</td>
<td>Ns △ SNCV</td>
<td>↓ IENFD</td>
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<tr>
<td></td>
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<td>(8 wks)</td>
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<tr>
<td>C57BL/6 db/db</td>
<td>24</td>
<td>Thermal analgesia</td>
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<td>Sullivan et al. 2007</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>↓ SNCV</td>
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<td>Ns △ MNCV</td>
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<td>Sullivan et al. 2007</td>
</tr>
<tr>
<td>C57BL/6 db/db</td>
<td>24</td>
<td>Thermal analgesia</td>
<td>↓ MNCV</td>
<td>↓ IENFD</td>
<td>Sullivan et al. 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ SNCV</td>
<td></td>
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</tr>
<tr>
<td>C57BL/6 ob/ob</td>
<td>11</td>
<td>Thermal analgesia</td>
<td>↓ MNCV</td>
<td>↓ IENFD</td>
<td>Drel et al. 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ SNCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C57BL/6 ob/ob</td>
<td>11</td>
<td>Tactile allodynia</td>
<td>↓ MNCV</td>
<td>↓ IENFD</td>
<td>Vareniuk et al. 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ SNCV</td>
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</table>

DRG, dorsal root ganglia; IENFD, intraepidermal nerve fiber density; MNCV, motor nerve conduction velocity; NCV, nerve conduction velocity; Ns △, no significant change; SNCV, sensory nerve conduction velocity.

Phenotyping was performed at final age unless indicated otherwise.
<table>
<thead>
<tr>
<th>Chow Fat</th>
<th>Chow supplier</th>
<th>Primary fat source</th>
<th>Strain</th>
<th>Sex</th>
<th>HFD initiation, wks</th>
<th>HFD duration, wks</th>
<th>Final age, wks</th>
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<th>NCV</th>
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<td>↓ IENFD</td>
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<tr>
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<td>12</td>
<td>24</td>
<td>Thermal hypoalgesia (6 wks)</td>
<td>↓ SNV</td>
<td>↓ IENFD</td>
<td>Coppey et al. 2011</td>
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<td>↓ MNCV</td>
<td>↓ SNV</td>
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<td>—</td>
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<td>↓ MNCV</td>
<td>↓ SNV</td>
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<td>—</td>
<td>Tactile allodynia</td>
<td>↓ MNCV</td>
<td>↓ SNV</td>
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</table>

HFD, high-fat diet; IENFD, intraepidermal nerve fiber density; MNCV, motor nerve conduction velocity; NCV, nerve conduction velocity; Ns ∆, no significant change; SNV, sensory nerve conduction velocity.

*Phenotyping was performed at final age unless indicated otherwise.
(Wright et al. 2007). Whereas C57BKS db/db mice have persistent hyperglycemia and develop robust neuropathy, db/db mice on the C57BL/6 background have transient hyperglycemia and absent or limited neuropathy (Dauch et al. 2012; Li et al. 2005; Sullivan et al. 2007; Wang et al. 2011). This suggests that the development and severity of DPN in this leptin-based T2DM model is strain-dependent. C57BL/6 db/db mice, however, do exhibit significant neurologic deficits when placed on a diet with an increased fat content (Sullivan et al. 2007).

Compared with db/db mice, neuropathy characterization in mice carrying the ob/ob mutation is relatively understudied. C57BL/6 ob/ob mice develop moderate hyperglycemia and hyperinsulinemia and are considered a model of obesity and mild T2DM. By 11 weeks of age, ob/ob mice exhibit nerve dysfunction, with decreased motor and sensory NCVs, thermal hypoalgesia and tactile allodynia, and abnormal anatomic morphology (Drel et al. 2006). These mice have several advantages over other models because they adequately model hypoalgesia and they display chronic hyperglycemia at a level that is physiologically relevant.

**Diet-Induced Obesity Mouse Models**

Prediabetes is now recognized as a key contributory factor associated with the development of idiopathic neuropathy in nondiabetic patients (Singleton et al. 2001); however, the pathogenic mechanisms underlying DPN development in the context of prediabetes remain undefined. Mice fed a high-fat diet (HFD) that subsequently develop diet-induced obesity (DIO) are instrumental in modeling the neurologic pathophysiology seen in prediabetes. Unlike db/db and ob/ob mice that are diabetic from 4 weeks of age and essentially bypass prediabetes, HFD-fed mice have a gradual onset of metabolic imbalances that are more characteristic of the human condition. Mice with DIO exhibit weight gain, increased adiposity, moderate hyperinsulinemia, and IGT but do not have elevated glucose levels (Coppey et al. 2011; Guilford et al. 2011; Obrosova et al. 2007; Vincent, Hayes et al. 2009).

As previously mentioned, the importance of diet was initially demonstrated in C57BL/6 db/db mice. When placed on regular chow (11.5% kcal from fat), the db/db mice are euglycemic and do not develop neuropathy; however, when placed on diet with moderately increased fat content (17% kcal from fat), the mice become strongly hyperglycemic and develop robust neuropathy (Sullivan et al. 2007). Diet alone can also sufficiently induce neuropathy in nondiabetic C57BL/6 mice (Obrosova et al. 2007). When fed an HFD consisting of 58% kcal from fat, mice developed hallmarks associated with prediabetes after 16 weeks, including increased weight gain, IGT, and normal levels of fasting glucose. Neuropathy was also present, as evidenced by decreased motor and sensory NCVs and impaired behavioral responses to mechanical and thermal stimuli.

Since these initial observations, several studies have investigated the effect of an HFD on the development of neuropathy in mice (Table 3). Collectively, these studies provide irrefutable evidence that increased dietary fat predisposes mice to nerve dysfunction in the absence of T2DM. However, it is important to note that minor discrepancies in the degree of neuropathy are also reported. These incongruities may be attributed to variations in neuropathy phenotyping approaches, differences in sex and age, differences in the duration of HFD feeding, and the source and percentage of fat content. Regarding sex-based differences, the Jackson Laboratory (www.jax.org) reports that male mice are more predisposed to DIO and gain weight more consistently than female mice. Furthermore, male and female mice develop different levels of pain, making comparisons of mechanical and thermal thresholds difficult between studies (Obrosova et al. 2007; Stavniichuk et al. 2010; Vincent, Hayes et al. 2009).

The severity of nerve dysfunction may also be dependent on the duration of HFD feeding (Guilford et al. 2011; Vincent, Hayes et al. 2009). Whereas a 54% HFD for 8 weeks promotes significant deficits in motor NCVs and tactile responses but no significant differences in sensory NCVs, thermal responses, or IENFD (Guilford et al. 2011), a 45% HFD for 34 weeks induces deficits in all measures of nerve dysfunction, with the exception of mechanical responses (Vincent, Hayes et al. 2009). The fat composition between these diets differed, however, and further investigation is required to determine the specific effects of HFD on nerve function because increased fat content and the source of fat both exacerbate obesity. Reports from the Jackson Laboratory indicate that increasing the percentage of dietary fat content induces greater levels of weight gain and insulin resistance in mice. HFD chow typically ranges 32–60% kcal from fat. In humans, 60% fat would be extreme, and although a lower percentage fat composition may provide a better representation of the human condition, higher percentage fat diets are often used to promote more rapid weight gain (Ghibaudi et al. 2002).

The type of fat also influences the severity of diabetes (Ikemoto et al. 1996; Wang et al. 2002). Mice readily develop obesity when placed on an HFD consisting primarily of saturated, obesogenic fat (e.g., lard, coconut oil), whereas mice on a diet of unsaturated fat (fish oil) do not gain as much weight (Ikemoto et al. 1996; Wang et al. 2002) and are more sensitive to insulin (Buettner et al. 2006). It is also important to keep in mind that diets composed of plant-derived ingredients may exhibit batch-to-batch variations reflective of changes in the growing season; thus, purified ingredients may offer improved consistency between studies for future cross-study data interpretation (Warden and Fisler 2008). Finally, chows may also contain phytoestrogens that reduce the degree of weight gain, so it is important that these components and micronutrients are carefully matched to those in control chow for DIO studies (Cederroth et al. 2007). With these potential considerations in mind, however, the DIO mouse model is advantageous in that it allows investigators to examine how particular dietary factors such as fat percentage and fat content exacerbate the neuronal phenotype.
It is currently unknown how differing fat percentages and content contribute to DPN because no studies have directly investigated these comparisons. The majority of neuropathic studies to date examining DPN in DIO mouse models have consistently used the C57/BL6 mouse model. The C57/BL6 mouse is quite susceptible to DIO, whereas other mouse strains on an HFD regimen have demonstrated more variable strain-dependent responses, or like C57BKS mice, are resistant to DIO (Survit et al. 1998). The Jackson Laboratory also reports that NON/ShiLtJ mice are quite sensitive to HFD-induced prediabetes and they attain a prediabetic state quicker than C57BL/6 mice, suggesting that neuropathy characterization may be warranted in this model. DIO mouse studies have, however, identified key metabolic abnormalities in peripheral nerve that accompany NCV, behavioral, and anatomical impairments. These include increased fructose and sorbitol as well as increased activity of the sorbitol pathway, increased oxidative and nitrosative stress, and increased poly (ADP-ribose) polymerase (PARP) activation in sciatic nerve, similar to changes observed in STZ-injected mice (Obrosova et al. 2007; Vincent, Hayes et al. 2009). Increased oxidative and nitrosative stress, characterized by increased immunoreactivity for 4-hydroxynonenal (4-HNE) adducts and nitrotyrosine, are present in both sciatic nerve and dorsal root ganglia (DRG) in these models (Obrosova et al. 2007). Notably, switching HFD-fed mice to a regular diet improved nerve function and decreased oxidative and nitrosative stress, both in the presence or absence of the antioxidant fiderostat (Obrosova et al. 2007). These results suggest that antioxidant therapy in combination with strict dietary control may augment the beneficial effects of a controlled diet and attenuate DPN progression.

Emerging Diabetes Mouse Models

Although many of the available T1DM and T2DM mouse models develop neurologic impairments associated with DPN, newer diabetic mouse strains are continually emerging in response to the need for models that more accurately mimic the human condition. For T1DM, the development of a “humanized mouse” enables a novel in vivo approach to study immunologic components of diabetes. Immunodeficient mice are engrafted with human β cells and components of human immune systems to recapitulate the T1DM environment present in patients (Brehm et al. 2012). These mice offer incredible potential for translational therapeutic studies.

The Jackson Laboratory is also developing numerous mouse models of T2DM, including polygenic NON/ShiLtJ, NONcNZO/LtJ, and TALLYHO/JngJ mice, that exhibit gradual diabetes onset similar to the human disease (detailed strain information is available through the Jackson Laboratory webinars and at www.jax.org). NON/ShiLtJ mice on an HFD are hyperglycemic and develop more severe obesity than C57BL/6 mice as well as increased insulin resistance. These mice have also been crossed by the Jackson Laboratory with NZO/HILtJ mice, a hyperphagic, obese, hyperinsulinemic mouse strain with IGT, to generate NONcNZO/LtJ mice. NONcNZO/LtJ mice develop hyperglycemia in the absence of obesity, with 56% of male mice exhibiting diabetes at 24 weeks of age (Reifsnyder et al. 2000). Further backcrossing of NONcNZO/LtJ mice with NON/ShiLtJ mice selected for multiple combinations of polygenic diabetes loci has resulted in various recombinant congenic strains, including NONcNZO10/LtJ mice that exhibit obesity, hyperinsulinemia, and IGT in 90–100% of male mice at 24 weeks of age (Leiter and Reifsnyder 2004). Finally, TALLYHO mice are useful to study diabetes onset and progression because they develop hyperinsulinemia around 6 weeks of age and hyperglycemia by 12 to 14 weeks of age in the presence of only modest obesity. Overall, these Jackson Laboratory models develop diabetes in the absence of severe obesity, representative of the clinical presentation in many patients, but neuropathy has not yet been assessed in these mice at this time.

Recent studies have also indicated that dyslipidemia is an important risk factor in DPN development, particularly in T2DM (Vincent, Hayes, et al. 2009; Wiggin et al. 2009); however, modeling dyslipidemia in diabetic mouse models is challenging because the lipid profile of mice is fundamentally different from that of humans. Whereas T2DM patients present with elevated levels of low-density lipoproteins and cholesterol, T2DM mice instead have an elevated high-density lipoprotein profile compared with control mice (Vincent, Hinder, et al. 2009). Thus, attempts to accurately model dyslipidemia in mice have used genetic manipulation to establish strains with a more physiologically relevant lipid profile. One such strain is the triple knockout ApoE–ApoB48–ob/ob mouse (Hinder et al. 2013). These mice more accurately model dyslipidemia in humans due to deficits in lipoprotein clearance; however, their usefulness to study DPN is limited because they present with only mild neuropathy (Hinder et al. 2013).

Insulin resistance and pancreatic β cell dysfunction that is present in humans is also being modeled in mice by combining an HFD with MLD-STZ treatment. The HFD regimen induces insulin resistance, and MLD-STZ treatment with low-to-moderate doses of STZ induces moderate levels of hyperglycemia in the presence of relatively normal levels of circulating insulin (Arunmozhi et al. 2008; Luo et al. 1998; Manchem et al. 2001). Mice exhibit hyperinsulinemia by 6 weeks of age after being on an HFD for 3 weeks and subsequently receive STZ over a 4 week period, with C57BL/6 ICR mice demonstrating an increased susceptibility to the diabetogenic effects of this approach compared with C57BL/6 mice (Luo et al. 1998). Although diabetic complications have not yet been examined in mice developed using this approach, rats exhibit many characteristic features of human diabetic nephropathy (Sugano et al. 2006), and the metabolic effects of various antiabetic and hypolipidemic agents have been assessed (Manchem et al. 2001).

Selecting an Appropriate Model

The development of DPN is undoubtedly multifactorial. Epidemiologic and in vivo studies suggest that factors
contributing to the severity of DPN include the duration of diabetes, diet, age, sex, and ethnicity, or the mouse genetic background (Aaberg et al. 2008; Kountz 2012). There is currently no single mouse model that accurately models human DPN in either T1DM or T2DM. It is therefore critical to choose a mouse model that most closely mimics the particular aspect of diabetes and DPN under investigation. Thus, clear experimental objectives as well as detailed experimental procedures must be determined before selecting an appropriate mouse model. Once selected, a comprehensive characterization of diabetes, the neuropathic phenotype, and the metabolic and physiologic profile are essential to completely understand the implications of the results on DPN pathogenesis. Here, we discuss important considerations that must be addressed when designing and selecting the appropriate mouse models for T1DM and T2DM DPN studies.

**T1DM Considerations**

Various mouse models of T1DM exist that mimic multiple aspects of diabetes, including (1) pathogen-induced, (2) spontaneous, (3) autoimmune, and (4) pharmacologic models (Van Belle et al. 2009). Mice that not only mimic the hallmarks of diabetes and DPN but also do so within a short length of time with minimal mouse-to-mouse variation are ideal. Thus far, the STZ-induced mouse model is the preferred T1DM model by investigators. Although SHD-STZ gives more pronounced diabetic phenotypes, the higher mortality attributed to nonspecific toxicity is a considerable disadvantage of this model. MLD-STZ, on the other hand, induces progressive β cell death that is more representative of T1DM. Thus, MLD-STZ is used extensively to study the immunologic response during insulinitis and β cell death (Karabatas et al. 2010; Mensah-Brown et al. 2002; Muller et al. 2002). Pancreatic β cell toxicity in mice, however, is strain-dependent, so careful dosage adjustments may be required to produce robust T1DM phenotypes. Spontaneous models have not been thoroughly explored because of the longer interval required for DPN onset and the high number of animals necessary to reach significance. Ongoing research efforts continue to develop more physiologically relevant mouse models to understand the etiology of T1DM (Van Belle et al. 2009); however, further characterization of the neuropathic phenotype in these models is needed before they are put to wider use.

**T2DM Considerations**

Because of the increasing prevalence of T2DM, significant time and resources have been invested in developing and characterizing accurate disease models. As with T1DM, when choosing a model of T2DM, it is important for the investigator to select a mouse model that accurately recapitulates the condition being investigated (i.e., the role of cholesterol, amount of fat in the diet, effects of unsaturated fatty acids, or prediabetes vs. frank diabetes). Leptin-based db/db and ob/ob mice are good models of frank diabetes because of the early onset and robust nature of neuropathy; however, some disadvantages do exist. First, leptin-based mouse models are often infertile, and generating significant numbers is time consuming. Second, C57BL/6 db/db and ob/ob mice have declining fasting blood glucose beginning at 4 weeks of age and do not maintain persistent hyperglycemia (Clee et al. 2005). Furthermore, deficient leptin signaling may have indirect consequences beyond those on the hypothalamus. Finally, the leptin-based models do not exhibit prediabetes. The emergence of HFD-fed models provides exciting new avenues for future investigations, and DIO mice that closely mimic key factors in human disease, such as nutrition and genetics, should continue to be explored. These mice exhibit dyslipidemia, insulinemia, and IGT but typically do not develop full-blown diabetes. This is representative of prediabetes in humans and suggests that these mice may be a significant model for studies addressing the underlying causes of diabetes and the potential benefits of early therapeutic interventions.

**Conclusions and Future Directions**

A considerable number of mouse models of T1DM and T2DM that exhibit neuropathy are available. Although these models have supported a number of studies and demonstrate neurological impairments (Tables 1–3), additional characterization of newer or more clinically relevant mouse models is warranted. For T1DM, the more common STZ-based models rely on pharmacologic toxicity to induce β cell destruction. NOD models have not yet been extensively characterized. Establishing a standard T1DM mouse model that exhibits robust neuropathy in a consistent manner is necessary. For T2DM, leptin-based models exhibit DPN, but potential systemic consequences of disrupted leptin signaling must also be considered. HFD mouse models may provide a better reflection of the human condition, but there is extensive variability in diet composition and regimens that complicates interstudy data comparisons. Thus, standardization of approaches to establish reproducible DIO mouse models and the development and characterization of non-leptin-based T2DM models is still needed. Furthermore, as DPN in humans is complex and likely multifactorial in origin, newer polygenic mice, such as TALLYHO and NON/NZO mice, may be ideal models for future DPN studies. Overall, there remains a critical need to explore and characterize novel mouse models that provide clinically relevant representations of human DPN, and a complete characterization of diabetes, the neuropathic phenotype, and the metabolic and physiologic profile are essential to completely understand the implications of DPN study results. Comprehensive phenotyping and standardization of disease induction approaches (particularly for DIO models) will be important steps in understanding how to gain the clearest insights into DPN pathogenesis and therapy design using animal models of T1DM and T2DM.
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attenuates neuron loss in the db/db mouse, a type 2 diabetes model.


