

Animal Models of Diabetic Neuropathic Pain

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Key words

- diabetes
- neuropathic pain
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Abstract

Diabetic neuropathy is a common complication of diabetes. It occurs in approximately 10–20% of patients with diabetes, or roughly 40–50% patients with diabetic neuropathy. However, the pathogenesis of diabetic neuropathic pain is still largely unknown. Several animal models have been used to study the underlying mechanisms for this complication. Some commonly used animal models include streptozotocin-induced rat and mouse models, diet/nutrition-induced models, combination of chemically- and nutrition-induced model, Zucker diabetic fatty rat model, type 1 insulinopenic BB/Wor and type 2 hyper-

insulinemic diabetic BBZDR/Wor rat models, and transgenic/knock-out models. Even though the manifestations of diabetic neuropathic pain vary from thermal or chemical hyperalgesia, thermal or chemical hypoalgesia, allodynia, to spontaneous pain, some pathogenesis factors are shared among these symptoms. Increased AR activity, oxidative-nitrosative stress, protein kinase C, PARP and ACE activations, C-peptide deficiency, impaired neurotrophism, and proinflammatory responses have been identified in the development of diabetic neuropathic pain. This review discusses selected animal models for diabetic neuropathic pain, as well as some commonly shared pathways in these models.

Introduction

Diabetes mellitus (DM) is the fourth or fifth leading cause of death in most developed countries (Richard et al., 2013). In many developing countries, there is substantial evidence showing that its prevalence is growing (Richard et al., 2013). Despite advancement in diabetes diagnosis, prevention, and treatment, in 2011, 34 million patients had diabetes worldwide (WHO, 2013). Diabetes complications could lead to disability, reduced quality of life, and death. In 2011, 4.6 million patients died of this disease (Richard et al., 2013).

Clinical manifestations of diabetes complications vary for different people; it may affect various parts of the body. In addition, no internationally agreed standards exist for diagnosing and assessing diabetes complications. Diabetic neuropathy is a common serious complication of diabetes. Approximately 50% of diabetes patients suffer from this complication (Diabetes in America 1995, Boulton 2004). Approximately 10–20% of patients with DM experienced painful symptoms, or roughly 40–50% patients with diabetic neuropathy had neuropathic pain (Veves et al., 2008).

Symptoms of neuropathic pain range from abnormal sensations such as paresthesia, allodynia, hyperalgesia, to spontaneous pain that could seriously affect quality of life (Calcutt 2002; Mondelli et al., 2012). Neuropathic pain was defined as pain that is initiated or caused by a primary lesion or dysfunction or transitory perturbation in the peripheral or central nervous system. It could be an increased responsiveness to different innocuous and painful mechanical, thermal, or chemical stimuli. (Merskey, Bogduk 1994; Devor, Seltzer 1999). Pathogenesis of diabetic neuropathic pain is mostly unknown. Some studies showed that impaired cutaneous endothelium-related vasodilation and C-fiber-mediated vasoconstriction as well as increased sural nerve epineurial blood flow may be associated with this complication. (Quattrini et al., 2007; Eaton et al., 2003; Bierhaus et al., 2012). Most knowledge of the disease pathogenesis has been gained from studies in diabetic rat and mouse models. The models that have been mostly studied include streptozotocin-induced rats and mice, high-fat diet-fed mice, combination of chemically- and nutrition-induced model, spontaneous or genetically derived model, including

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Zucker diabetic fatty rats, type 1 insulinopenic BB/Wor and type 2 hyperinsulinemic diabetic BBZDR/Wor rats, nonobese diabetic, Akita mice, and leptin- and leptin-receptor-deficient mice. Some techniques have been used to assess the behavioral responses to external stimuli in diabetic animals (i.e., thermal and mechanical hyper- and hypoalgesia, tactile allodynia, as well as formalin-induced spontaneous nociceptive behavior). This review focuses on the discussion of selected animal models that have been proven to be useful in studying the underlying mechanisms of diabetic neuropathic pain.

Streptozotocin-Induced Diabetic Rats and Mice

Streptozotocin (2-deoxy-2(3-methyl-3-nitrosoareido)-D-glucopyranose) is a nitrosourea analogue. It is toxic to the pancreatic insulin-secreting β -cells by damaging its DNA (Szkudelski 2001; Lenzen et al., 2008). It is similar to glucose and could be transported via glucose transporter GLUT2. The nitrosoamide moiety of streptozotocin is responsible for its toxicity. The establishment of streptozotocin-induced diabetes model is relatively simple, with one time injection either intraperitoneally or intravenously. Therefore, the streptozotocin-induced diabetic rat has been widely used to study mechanism of diabetic neuropathic pain and to evaluate potential therapies.

Various doses of streptozotocin (35–200 mg/kg in rats or mice) have been studied in animal models (Srinivasan, Ramarao 2007; Jafarnejad et al., 2008). The susceptibility of animal to streptozotocin depends on age, species, and strain. Different dosages may lead to different levels of β -cell impairment in pancreas. Higher dose streptozotocin injection induced diabetes is similar to type I insulin-dependent diabetes in humans: within 72 h of injection, most rats become hyperglycemic, lowered glucose-stimulated insulin secretion, and decreased glucose intolerance. In about 41/2 weeks after injection, streptozotocin-treated rats exhibit behavioral signs of diabetic neuropathic pain, including significant reduction in the withdrawal threshold to mechanical pressure and the latency to withdrawal from a noxious thermal stimulus (Morrow, 2004).

Animal model of type 2 diabetes has been induced by combination of streptozotocin and nicotinamide (NA) administration in adult rats. NA is administered to partially protect insulin-secreting β cells against streptozotocin. The protective mechanism is thought to partially due to the inhibition of PARP-1 activity, preventing depletion of NAD^+ and ATP in the cells exposed to streptozotocin. The severity of diabetes in this animal model depends on the doses of streptozotocin and NA. The hyperglycemia level could range from mild to severe (Szkudelski, 2012).

Interestingly, studies showed that a single injection of streptozotocin (80–100 mg/kg) into neonatal rats or immediately after birth, those rats will develop type II diabetes in the adult age (Bonner-Weir et al., 1981; Portha et al., 1994). Rats with short-term diabetes develop neuropathic pain, whereas those with longer-term diabetes and diabetic mice typically display manifestations of both painful and insensate neuropathy, or insensate neuropathy only (Obrosova, 2009).

Thermal hyperalgesia is an increased sensitivity to pain, which may be caused by damage to nociceptors or peripheral nerves. It has been studied in streptozotocin induced animals with short-term (2–8 weeks) diabetes (Calcutt et al., 2004; Cameron et al., 2001; Cameron et al., 2001; Li et al., 2005). The underlying

mechanisms have been identified to be related to increased aldose reductase (AR), protein kinase C (PKC), poly (ADP-ribose) polymerase (PARP), angiotensin converting enzyme (ACE) activities, toll-like receptor 4, and oxidative stress (Meller et al., 1992; Cotter et al., 2002; Obrosova et al., 2008; Yan et al., 2012). It was shown that subsequent activation of soluble guanylate cyclase in the lumbar spinal cord could mediate thermal hyperalgesia. Increased excitability of dorsal root ganglion neurons and expression of Nav1.7 and p-EPK1/2 has been identified in thermal hyperalgesia (Zhang et al., 2013). In addition, methylglyoxal treatment for thermal hyperalgesia could induce post-translational modification of the nociceptor-specific sodium channel Nav 1.8, reduce nerve conduction velocity, neurosecretion of calcitonin gene-related peptide, and increase cyclooxygenase-2 (COX-2) expression (Bierhaus, Nawroth 2012). In a chemical hyperalgesia induced by formalin in streptozotocin animal model, it has also been shown that peripheral activation of CB1 and CB2 receptor mediate the antinociceptive effect of exogenous and endogenous anandamide (Schreiber et al., 2012).

Thermal hypoalgesia occurs when nociceptive stimuli are interrupted or decreased in the pathway. It is a clinical manifestation in patients with advanced diabetic neuropathy. This condition has been studied in long-term streptozotocin-induced diabetes models (Calcutt et al., 2004; Cameron et al., 2005). Interestingly, most above mentioned mechanisms for the increased thermal sensitivity in the short-term animal models were also involved in long-term thermal hypoalgesia development. For example, increased AR activity, activation of the AGE/RAGE axis, oxidative-nitrosative stress, as well as activation of ACE, and PARP were identified in thermal hypoalgesia (Calcutt et al., 2004; Li et al., 2005; Cameron et al., 2005; Ilnytska et al., 2006; Drel et al., 2007; Vareniuk et al., 2008; Francis et al., 2008; Sumner et al., 2003). In addition, studies showed that neurotrophic factor deficiency may as well contribute to diabetes-induced thermal sensory loss (Sumner et al., 2003). Epidermal nerve fiber loss is evident in both type 1 and type 2 diabetic patients Pittenger et al., 2004; Shun et al., 2004; Drel et al., 2007). In streptozotocin-induced diabetic animal models, reduced intraepidermal nerve fiber density was seen (Yan et al., 2012). However, it has been shown that hypoalgesia could be developed before small sensory nerve fiber degeneration (Beiswenger et al., 2008; Dobretsov et al., 2003). Studies showed that after streptozotocin injection, onset of hypersensitivities of mechanical stimuli could emerge as early as 1 week and mechanical hyperalgesia could be fully developed by 2–8 weeks (Chen, Pan 2002; Courteix et al., 1993; Malcangio et al., 1998). However, at least 6–10 months streptozotocin-induced diabetes are required for nerve morphological and functional abnormalities, including changes in nerve microvessel and conduction velocity, to become apparent, suggesting the development of hyperalgesia may parallel or follow the development of hyperglycemia, metabolic and/or circulatory abnormalities in the streptozotocin diabetic models (Benstead, Sangalang 1995; Kalichman et al., 1998; Qiang et al., 1998). Streptozotocin-induced diabetic animal models have also been used to study mechanical hyperalgesia and hypoalgesia. Elevated mechanical withdrawal thresholds in these models were associated with AR, oxidative stress, and PARP (Calcutt et al., 2004; Cameron et al., 2005; Dobretsov et al., 2007; Xu et al., 2012). It has been shown that in a mechanical hyperalgesia model, galanin receptor 1 expression was decreased in spinal dorsal horn and galanin receptor 2 expression was decreased in both dorsal root ganglion and spinal dorsal horn. Furthermore,

galanin receptor 1 has been involved in the effect of attenuation of diabetic neuropathic pain (Xu et al., 2012). Methylglyoxal induces post-translational modification of the nociceptor-specific sodium channel Nav 1.8 is involved in mechanical hyperalgesia (Francis et al., 2009).

Allodynia is the pain due to a stimulus that does not normally provoke pain. This condition occurs in approximately 30–50% of patients with DM (Vinik et al., 1995; Bastyr et al., 2005). However, it has not been studied in animal models as extensively as hyperalgesia or hypoalgesia. In one streptozotocin-induced diabetic mouse model, nocifensive behaviors are evoked by light touch of von Frey filaments to the paw (15g) (Chaplan et al., 1994). Nitrosative stress, PARP activation, increased excitability of dorsal root ganglion neurons and expression of Nav1.7 and p-EPK1/2 were thought to be associated with allodynia (Cameron et al., 2005; Ilnytska et al., 2006; Drel et al., 2007; Obrosova 2007). In another mechanical allodynia model, activation of both CB1 and CB2 has been shown to be involved in cannabinoid-induced relief of neuropathic pain (Vera et al., 2012).

Streptozotocin-induced diabetic rat models have been studied for understanding spontaneous inflammatory nociceptive behaviors which display exaggerated flinching behavior in both the first and second phases of the formalin test (Ilnytska et al., 2006). Several pathogenetic mechanisms have been identified, including increased activities of AR, PARP, and cyclooxygenase-299, as well as decreased neurotrophic support; and changes in signaling of GABA and potassium-chloride cotransporters (Cameron et al., 2005; Ilnytska et al., 2006; Ramos et al., 2007; Jolivalt et al., 2008; Jolivalt et al., 2008).

Some insights have been gained by testing antinociceptive agents in streptozotocin-induced diabetic animal models. For example, it has been shown that enhanced Rab7 lysosomal targeting of μ -opioid receptors leads to loss of opioid antinociception in diabetic neuropathic pain. In addition, activation of muscarinic cholinergic receptors in the forebrain, and an increased expression of type-2 metabotropic glutamate receptors in dorsal root ganglia neurons were identified in analgesia process of acetyl-L-carnitine. The process is thought to be mediated by acetylation of transcription factors of the nuclear factor (NK)- κ B family (Mousa et al., 2013; Chiechio et al., 2007).

Overall, streptozotocin-induced diabetic animal models have been widely studied to understand diabetic neuropathic pain. The mechanism underlying hyperalgesia and abnormal sensation were identified as increased AR activity, oxidative-nitrosative stress, protein kinase C, PARP and ACE activations, C-peptide deficiency, impaired neurotrophism, and proinflammatory response (Meller et al., 1992; Cotter et al., 2002; Cameron et al., 2005; Ilnytska et al., 2006).

Diet/Nutrition Induced Diabetic Animal Models

In these models, rats or mice develop diabetes associated with obesity as a result of over nutrition, which mimic the metabolic syndrome in humans, and most require long period of dietary treatment. Sand rat, Tuco-Tuco and Spiny mouse are some models of diet/nutrition induced obesity and type 2 diabetes (Shafir 2003).

In C57BL/6J mice, type 2 diabetes was induced by simply feeding the mice with high fat diet. This mouse model is characterized with increased obesity, insulin resistance, hyperinsulinemia and increased serum total cholesterol levels (Surwit et al., 1988). In

addition, baseline and fasting hyperglycemia were shown. These mice have been shown to develop peripheral leptin resistance.

Sand rat: *Psammomys obesus* (*P. obesus*; Sand rat) develop obesity and type 2 diabetes when fed on high energy diet (Shafir et al., 1999). The sand rats develop hyperphagia, obesity, glucose intolerance and hyperinsulinaemia. Eventually, these rats can develop β cell degeneration and necrosis, insulin deficiency, overt diabetes and ketosis that could lead to death.

Decreased 2 deoxyglucose uptake and GLUT-4 protein and restrain hepatic gluconeogenesis were demonstrated with elevated phosphoenolpyruvate carboxykinase (PEPCK) activity. Increased proinsulin to insulin ratio in pancreatic β cells was shown. Insulin support was required for survival of Sand rats at a late stage.

In C57BL/6J (*ob/ob*) mouse, onset of symptoms is genetically determined. When treated orally with, LAF237, an inhibitor of dipeptidyl peptidase-IV, these mice showed normalized glucose tolerance in association with augmented insulin secretion (Winzell, Ahren 2004).

In addition, *Acomys calirinus* (spiny mouse) showed weight gain and pancreatic β cell hyperplasia, hypertrophy and increased pancreatic insulin content when on high energy diet. An impairment hormone release mechanism was demonstrated in these mice (Velasquez et al., 1990). These mice develop frank hyperglycemia with glucosuria leading to fatal ketosis.

Ctenomys talarum (Tucotuco) exhibits similar manifestations as sand rat and spiny mice when fed high energy diet. (Vogel, Vogel 1997) Peripheral neuropathy and, predominantly, small sensory fiber neuropathy, have been reported (Sumner et al., 2003; Pit-tenger et al., 2005; Papanas et al., 2011).

Diet/nutrition induced diabetic animal models have been studied for diabetic neuropathic pain. It was shown that a high-fat diet-fed mouse manifested alimentary obesity, hyperinsulinemia, and impaired glucose tolerance, leading to nerve conduction velocity deficit and small sensory fiber neuropathy, as well as increased sorbitol pathway activity, oxidative-nitrosative stress, and pro-inflammatory changes in PNS. More specifically, increased lipoxigenase activity has been implicated in endothelial dysfunction, an important factor in motor and sensory nerve conduction velocities deficits that associated with both diabetic and prediabetic neuropathy. In addition, lipoxigenase has been shown to be involved in high-fat-diet-induced inflammation (Cameron et al., 2001; Natarajan and Nadler 2003; Natarajan and Nadler 2004; Low et al., 1997; Cameron et al., 1997; Nakamura et al., 1999; Yagihashi et al., 2001; Obrosova et al., 2002). A major limitation to this approach is that most diet/nutrition induced diabetes animal models required long period time for induction. Therefore, these models are considered as long-term high-fat diet models.

Models Induced by Combination of Diet/Nutrition and Streptozotocin

Various studies showed the benefits of using the combination of nutrition- and streptozotocin-induced animal model. By using a combination of a high-fat diet and a streptozotocin inducer, diabetes can be induced more quickly. Different levels of high-fat diet and streptozotocin combinations have been studied. Some contain higher fat diet-fed and streptozotocin (30% of high fat diet and 15 mg/kg of streptozotocin) (Zhang et al., 2003). Even

though it takes a longer time to develop diabetes, these animals develop hyperglycemia, hyperinsulinemia, impaired glucose tolerance, insulin resistance and dyslipidemia. When lower fat diet-fed and higher-dose streptozotocin were used (7% and 65 mg/kg, respectively), it takes relatively shorter time to develop hyperglycemia, hyperinsulinemia, moderate insulin resistance, dyslipidemia and increased liver glycogen levels (Islam and Choi, 2007). However, total cholesterol and low density lipoprotein-cholesterol (LDL-C) levels are not as high as those with higher high-fat diet. When using higher high-fat-diet-fed plus higher-dose of streptozotocin animal models (40% and 50 mg/kg), increased body weight, fasting blood glucose, triglyceride and free fatty acid levels were developed (Reed et al., 2000). Moderate high-fat diet-fed and moderate dose of streptozotocin animal models were used in some studies (20% and 40 mg/kg) (Luo et al., 1998).

Zucker diabetic fatty rat model

The Zucker diabetic fatty (ZDF) is an outbred rat model that spontaneously progresses to frank diabetes due to failure to compensate adequately for insulin resistance. The homozygous mutation (*fa/fa*) of the leptin hormone receptor is involved in the development of type 2 diabetes in male rats when they are fed a high-energy rodent diet (Hemmes and Schoch, 1988). Obese ZDF rats could have high levels of triglyceride and cholesterol. By using high saturated fat and sucrose-containing diets, very high lipid levels can be induced. In ZDF rats, the pancreatic islets were shown to have increased intraislet expression of ACE and angiotensin type 1 as well as increased intraislet fibrosis, apoptosis, and oxidative stress (Siwy et al., 2012). In addition, examination of ZDF rat somatic (sciatic) nerve has shown evidence of neuropathy similar to streptozotocin-rats as characterized by reduced conduction velocity and morphological changes in myelinated axons (Schmidt et al., 2003). It was reported that increased ACE and hydroxymethylglutaryl-CoA reductase activities, and neutral endopeptidase might be involved in sensory loss in Zucker fatty rats (Oltman et al., 2009; Oltman et al., 2008).

BBZDP/Wor rat

In addition to encoding the *Leprfa* mutation in ZDF rats, the BBZDP/Wor strain carries the *Iddm2* type 1 diabetes associated genetic locus (Mordes et al., 2004). BBZDP/Wor rats develop lymphopenia, obesity, hyperinsulinemia, and autoimmune diabetes (Guberski et al., 1988). It is believed that BBZDP/Wor rat develop diabetes due to a combination of insulin resistance and autoimmune insulinitis. Therefore, both type 1 and type 2 diabetes characteristics exist in this model.

BBZDR/Wor rat

BBZDR/Wor type 2 diabetic rat was developed by crossing BBZDP/Wor animals with the lean, nondiabetic BBDR/Wor rats, in order to remove the recessive *Iddm2* gene responsible for lymphopenia and spontaneous autoimmunity and retain the *Leprfa* (*fa1*) mutation. Therefore, the BBZDR/Wor rat is an inbred rat model for type 2 diabetes. BBZDR/Wor diabetic rat has been shown to have dyslipidemia, hyperglycemia, insulin resistance, hypertension, and decreased levels of the β cell-specific glucose transporter type-2 (GLUT-21) (Ellis et al., 1998). Furthermore, reduction of GLUT-2 staining of β -cell surface membranes has been observed.

The type 2 diabetic BBZDR/Wor and type 1 diabetic BBDP/Wor rat models have been studied for diabetic neuropathy. These 2

models show similarities and differences of disease pathogenesis. Progressive reduction of nerve conduction velocity, axonal atrophy, and degeneration, inactivation of Na^+ -channels, intra-axonal Na^+ accumulation at the node, decreased Na^+/K^+ -ATPase, and nerve degeneration have been evident in both models. However, the slowing of nerve conduction velocities has been shown to be more severe in BBZDP/Wor rats than in BBZDR/Wor rats. On the other hand, BBZDR/Wor rats display a more severe Na^+/K^+ -ATPase defect. In BBZDP/Wor type 1 diabetes, disruption of the paranodal ion-channel barrier by axoglial dysjunction and paranodal demyelination have been demonstrated. While in BBZDR/Wor rats with type 2 diabetes, these structural changes have not been observed. Also, studies have shown that the perturbed insulin signaling due to insulin and/or C-peptide deficiency in type 1 BBDP/Wor rats may account for the differences seen between these 2 diabetic models (Sima and Sugimoto, 1999; Sima et al., 2000). While in BB/Wor type 2 diabetes model, whole-cell, high-threshold, voltage-dependent calcium currents were enhanced in acutely dissociated, capsaicin-sensitive dorsal root ganglion neurones (Hall et al., 1995).

In a mechanical allodynia type 2 diabetic ZDF model, activation of CB1 has been shown to be involved in cannabinoid-induced relief of neuropathic pain (Obrosova et al., 2007). Another interesting finding is the reduced intraepidermal nerve fiber density in ZDF models (Oltman et al., 2008).

Transgenic/Knock-out Diabetic Models



It has been shown that the behavioral changes of neuropathic pain in transgenic/knock-out diabetic models are strongly influenced by the specific knock-down of certain receptors such as the P2X3 receptor. In one animal model, 7 days after spinal nerve ligation, interestingly, the P2X3 receptor expression was decreased in small diameter neurons of the L5-L6 DRG. However, the increase was not found in large diameter neurons in L5-L6 DRG as well as in both small and large diameter neurons in L4 DRG. Inhibitor RNA (iRNA) techniques may be used in future studies to reduce the compensatory genetic alternatives in knock-out animals (Kage et al., 2002).

Limitations



Currently, available treatments for diabetic neuropathic pain are far from effective. Diabetic animal models have been widely used to identify new targets for diabetic neuropathic pain treatment. Even though models for studying diabetic neuropathic pain has identified a number of pathogenetic mechanisms implicated in diabetic painful and insensate neuropathy, the current models still have some limitations for diabetic neuropathic pain studies. Firstly, the life span of animal models is limited without obvious neuropathy. It is especially challenging to study how demyelination, axonal degeneration, fiber loss, or axonal regeneration contribute to diabetic neuropathic pain develop and progress. In addition, quantification of spontaneous pain in animals is technically challenging. Combination of multiple modalities, including streptozotocin and diet-nutrition, may be able to produce a more sophisticated animal model for diabetic neuropathic pain. In addition, gene expression profiling was explored for changes in mRNA transcripts in the dorsal root

	Onset of diabetes	Hyperglycemia	Insulin resistance	BW	TC	TG
STZ-induced	short	yes	no	↓	±	±
high fat diet	long	yes	yes	↑	↑	↑
high fat diet/STZ	long	yes	yes	↑ ↓		↑
transgenic/knockout	short	yes	yes	↓		

BW: body weight; TC: total cholesterol; TG: triglycerides

Table 1 Characteristics of diabetic animal models.

ganglia and dorsal horn across multiple models of peripheral neuropathic pain. Further, sophisticated tools that have been developed and used in clinical studies including quantitative measurement of symptoms and signs and quantitative sensory testing may be adapted into animal models (Tegeer et al., 2006; Bennett et al., 2007; Hansson et al., 2007).

In conclusion, various animal models have been used to understand the mechanism underlying pathogenesis of diabetic neuropathic pain (Table 1). Some commonly shared pathways have been identified in the development of diabetic neuropathic pain, including increased AR, PKC, and PARP activities, nonenzymatic glycation/glycoxidation, and oxidative stress. However, pathogenesis of painful diabetic neuropathy is still waiting for further investigations. Identifying particular neurobiological mechanisms contributing to neuropathic pain in individuals and development of more sophisticated tools for measuring and categorizing neuropathic pain may advance the progress of diabetic neuropathic pain animal models.

Conflict of interest: None.

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