Bench Evidence for Diabetic Peripheral Neuropathy: What does Animal Studies Inform Clinical Practice?

Kumar Senthil P., Adhikari Prabha, Jeganathan

[1]Founder-President, Academy of Orthopaedic Manual Physical Therapists (AOMPT)TM, Freelancer Physiotherapist and private practitioner, Mangalore, [2]Professor, Department of Medicine, [3]Professor, Department of Physiology, Kasturba Medical College (Manipal University), Mangalore, Karnataka, India.

(Received on 20.06.2013; Accepted on 08.11.2013)

Abstract

This short communication was aimed at enumerating the evidence from animal models of Diabetic peripheral neuropathy (DPN) in order to imply clinical decision-making in routine practice through a preliminary search of PubMed. The animal models demonstrated abnormalities in motor nerve conduction velocity (MNCV) and hind-limb digital sensory nerve conduction velocity (SNCV) deficits, thermal hypoalgesia, tactile allodynia, and a remarkable loss of intraepidermal nerve fibers. The streptozotocin (STZ)-induced diabetic rat is the most commonly employed animal model used to study mechanisms of painful diabetic neuropathy through behavioral assays of mechanical allodynia and heat hyperalgesia and to evaluate potential therapies.

Keywords: Bench-to-bedside; Knowledge translation; Evidence-based practice; Animal sciences.

Corresponding author: Senthil P Kumar, Founder-President, Academy of Orthopaedic Manual Physical Therapists (AOMPT)[TM] , Freelancer Physiotherapist and private practitioner, Mangalore, India.

E-mail: senthilparamsivamkumar@gmail.com

© Red Flower Publication Pvt Ltd

This short communication was aimed at enumerating the evidence from animal models of Diabetic peripheral neuropathy (DPN) in order to imply clinical decision-making in routine practice through a preliminary search of PubMed.

Historically, animal models of DPN studied streptozotocin-induced diabetic rats and mice forfunctional, metabolic, neurotrophic, and morphological abnormalities for type-1 diabetes, and leptin-deficient (ob/ob) mice for type-2 diabetes.[1] The animal models demonstrated abnormalities in motor nerve conduction velocity (MNCV) and hind-limb digital sensory nerve conduction velocity (SNCV) deficits, thermal hypoalgesia, tactile allodynia, and a remarkable loss of intraepidermal nerve fibers.[2]

Animal models and biomarkers of DN have been extensively used in neuropathic research. Diabetic rodents show behavioral, functional, structural and molecular biomarkers and they are widely used as models to investigate the etiology of DN as well as to screen the efficacy of the potential therapeutic interventions.[3] The streptozotocin (STZ)-induced diabetic rat is the most commonly employed animal model used to study mechanisms of painful diabetic neuropathy through behavioral assays of mechanical allodynia and heat hyperalgesia and to evaluate potential therapies.[4]

Analysis of slow axonal transport in BB rats revealed a delay in transport of the neurofilament (NF) subunits, tubulin, actin, and the 60, 52, and 30 kDa polypeptides in both systems. Morphometric analysis revealed that the cross-sectional area of axons was also increased proximally at the level of the motor roots and decreased distally. The changes in slow transport and caliber observed in central and peripheral axonal systems of diabetic BB rats are virtually identical to those previously described in rats with streptozotocin-induced diabetes.[5]

The bradykinin system was hypothesized to mediate hyperalgesia through the inducible bradykinin B1 receptor subtype which was evidenced by the efficacy of selective antagonists of the inducible bradykinin B1 receptor (BKB1-R) subtype.[6] In addition to dissociated cell culture of peripheral neurons (mainly DRG neurons) and Schwann cells, and explant culture of peripheral ganglia and retinas on diabetic animals or patients, adult animal neurons and Schwann cells were also cultured under high glucose conditions and adult animal neurons exposed to diabetic serum in order to study inter-relationship.[7]

Vincent *et al* demonstrated that overexpression of superoxide dismutase (SOD2) decreases superoxide (O(2)(-)) in cultured primary dorsal root ganglion (DRG) neurons and subsequently blocks caspase-3 activation and cellular injury; and underexpression of SOD2 in dissociated DRG cultures from adult SOD2(+/-) mice results in increased levels of O^{2-}, activation of caspase-3 cleavage and decreased neurite outgrowth under basal conditions that are exacerbated by hyperglycemia. SOD2 activity thus was an important cellular modifier of neuronal oxidative defense against hyperglycemic injury.[8]

Vincent *et al* explained the role of imbalance between mitochondrial biogenesis and fission in the pathogenesis of DPN, "During acute hyperglycemia, mitochondrial fission is a prominent response, and excessive mitochondrial fission may result in dysregulation of energy production, activation of caspase 3, and subsequent DRG neuron injury. During more prolonged hyperglycemia, there is evidence of compensatory mitochondrial biogenesis in axons."[9]

Wuarin-Bierman *et al* studied pain threshold and MNCV in three animal models of diabetic and nutritional neuropathies: Psammomysobesus (sand rat), streptozotocin-treated and galactose-fed rats. 75 rats were controls, 16 were hyperinsulinaemic, 46 were insulin-deficient and 12 were galactosaemic animals. The study confirmed that hyperalgesia was a constant feature of sensory dysfunction in spontaneous and experimental models of diabetic neuropathy.[10]

Kitahara *et al* examined the effect of long-term suppression of postprandial hyperglycemia and glycemic fluctuation in Goto-Kakizaki (GK)

rats, a type 2 diabetic animal model, by nateglinide (NG), a fast-acting hypoglycemic agent, and the slow-acting effect of glibenclamide (GC). The study findings suggested that meticulous control of postprandial hyperglycemia is essential to inhibit the development of neuropathy in type 2 diabetes.[11]

Wang et al compared four different herpes simplex virus (HSV)1-based vectors to produce one of two opioid receptor agonists (enkephalin or endomorphin), or one of two isoforms of glutamic acid decarboxylase (GAD65 or GAD67), alone and in combination, in the streptozotocin-induced diabetic rat and mouse models. The study found that a single subcutaneous hindpaw inoculation of vectors expressing GAD65 or GAD67 reduced diabetes-induced mechanical allodynia and thermal hyperalgesia which demonstrated that either GAD65 or GAD67 vectors are the most effective in the treatment of diabetic pain.[12]

The animal models demonstrated abnormalities in motor nerve conduction velocity (MNCV) and hind-limb digital sensory nerve conduction velocity (SNCV) deficits, thermal hypoalgesia, tactile allodynia, and a remarkable loss of intraepidermal nerve fibers. The streptozotocin (STZ)-induced diabetic rat is the most commonly employed animal model used to study mechanisms of painful diabetic neuropathy through behavioral assays of mechanical allodynia and heat hyperalgesia and to evaluate potential therapies.

References

1. Drel VR, Mashtalir N, Ilnytska O, Shin J, Li F, Lyzogubov VV, Obrosova IG. The leptin-deficient (ob/ob) mouse: a new animal model of peripheral neuropathy of type 2 diabetes and obesity. *Diabetes.* 2006; 55(12): 3335-43.
2. Jakobsen J, Lundbaek K. Neuropathy in experimental diabetes: an animal model. *Br Med J.* 1976; 2(6030): 278-9.
3. Shaikh AS, Somani RS. Animal models and biomarkers of neuropathy in diabetic rodents. *Indian J Pharmacol.* 2010; 42(3): 129-34.
4. Morrow TJ. Animal models of painful diabetic neuropathy: the STZ rat model. *Curr Protoc Neurosci.* 2004; Chapter 9:Unit 9. 18.
5. Medori R, Jenich H, Autilio-Gambetti L, Gambetti P. Experimental diabetic neuropathy: similar changes of slow axonal transport and axonal size in different animal models. *J Neurosci.* 1988; 8(5): 1814-21.
6. Gabra BH, Berthiaume N, Sirois P, Nantel F, Battistini B. The kinin system mediates hyperalgesia through the inducible bradykinin B1 receptor subtype: evidence in various experimental animal models of type 1 and type 2 diabetic neuropathy. *Biol Chem.* 2006; 387(2): 127-43.
7. Sango K, Saito H, Takano M, Tokashiki A, Inoue S, Horie H. Cultured adult animal neurons and schwann cells give us new insights into diabetic neuropathy. *Curr Diabetes Rev.* 2006; 2(2): 169-83.
8. Vincent AM, Russell JW, Sullivan KA, Backus C, Hayes JM, McLean LL, *et al.* SOD2 protects neurons from injury in cell culture and animal models of diabetic neuropathy. *Exp Neurol.* 2007; 208(2): 216-27.
9. Vincent AM, Edwards JL, McLean LL, Hong Y, Cerri F, Lopez I, *et al.* Mitochondrial biogenesis and fission in axons in cell culture and animal models of diabetic neuropathy. *Acta Neuropathol.* 2010; 120(4): 477-89.
10. Wuarin-Bierman L, Zahnd GR, Kaufmann F, Burcklen L, Adler J. Hyperalgesia in spontaneous and experimental animal models of diabetic neuropathy. *Diabetologia.* 1987; 30(8): 653-8.
11. Kitahara Y, Miura K, Takesue K, Mine T, Wada R, Uchida Y, Ito S, Yagihashi S. Decreased blood glucose excursion by nateglinide ameliorated neuropathic changes in Goto-Kakizaki rats, an animal model of non-obese type 2 diabetes. *Metabolism.* 2002; 51(11): 1452-7.
12. Wang Y, Nowicki MO, Wang X, Arnold WD, Fernandez SA, Mo X, *et al.* Comparative effectiveness of antinociceptive gene therapies in animal models of diabetic neuropathic pain. *Gene Ther.* 2012 Dec 13. doi: 10.1038/gt.2012.90. [Epub ahead of print].