International Physiology
Short Communication Vol.1 No.1, January - June 2013

Role of Neurotrophic and Nerve growth factors in Physiology, Pathology and Treatment of Diabetic Peripheral Neuropathy (DPN)

Kumar Senthil P.*, Adhikari Prabha, Jeganathan*****

Abstract

Neurotrophic factors were first reported in 1950s, and are widely acclaimed for their ability to provide effective therapy for untreatable neurodegenerative disorders.Diabetic peripheral neuropathy (DPN) is a common microvascular complication of diabetes mellitus (DM) and is acclaimed as a potentially untreatable neurodegenerative peripheral nerve disorder due to structural and functional changes in lower extremity nerves. Although existing evidence suggested alterations in nerve growth factor levels in experimental DPN, it is yet to be established whether observed growth factor deficiencies were due to decreased synthesis, or functional, e.g. an inability to bind to their receptor, and/or abnormalities in nerve transport and processing. Recombinant human nerve growth factor (rhNGF) was extensively studied and reported for its efficacy in animal studies of DPN.

Keywords: Neurotrophins; Neurotrophism; Nerve growth factors; Diabetic neuropathy.

Neurotrophic factors were first reported in 1950s, and are widely acclaimed for their ability to provide effective therapy for untreatable neurodegenerative disorders. The first neurotrophic factor to be discovered was Nerve growth factor (NGF), which was selectively trophic for small fiber sensory and sympathetic neurons.[1] The other factors were brain-derived neurotrophic factor, neurotrophin [NT]-3, and NT-4/5), and insulin-like growth factor (IGF)-I and IGF-II, and glial cell-derived neurotrophic factor.[2]

Neurotrophic factors have physiological effects on neurons such as inducing morphological differentiation, enhancing nerve regeneration, stimulating neurotransmitter expression, and otherwise altering the physiological characteristics of neurons.[3] Studying neurotrophic and other nerve growth factors is essential in a commonly "difficult-to-treat" neuropathic pain condition such as diabetic peripheral neuropathy (DPN).[4]

One contributing factor in DPN was an altered neurotrophism that resulted from changes in the synthesis and expression of neurotrophins, insulin-like growth factor, and various cytokine-like growth factors that could directly act upon distinct subpopulations of sensory and motor neurons.[5] Neurotrophins and other growth factors or inflammatory mediators influence neurons and axons in diabetic peripheral neuropathy (DPN) and these substances prevent loss of diabetic dorsal root ganglion (DRG) cells or enhance regeneration of diabetic nerves.[6]

"Pre-clinical studies in animal models of DPN have demonstrated the likely efficacy of factors such as NGF for small-fibre sensory neuropathy, BDNF, CNTF and IGF-I for motor neurone disease, and NT-3 for large-fibre neuropathy."[7] Tomlinson *et al*[8] found, "in rodent models of diabetes,

Author's Affiliations: *Founder-President, Academy of Orthopaedic Manual Physical Therapists (AOMPT)™ , Freelancer Physiotherapist and private practitioner, Mangalore, India, **Professor, Department of Medicine, ***Professor, Department of Physiology, Kasturba Medical College (Manipal University), Mangalore, India.

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

E-mail: senthilparamasivamkumar@gmail.com

(Received on 29.04.2013, Accepted on 08.05.2013)

©Red Flower Publication Pvt. Ltd.

there were expression deficits in nerve growth factor (NGF) and in mRNA for its high-affinity receptor, trkA, leading to decreased retrograde axonal transport of NGF and decreased support of NGF-dependent sensory neurons, with reduced expression of their neuropeptides, substance P and calcitonin gene-related peptide (CGRP)."

"Nerve regeneration or sprouting in diabetes may occur not only in the nerve trunk but also in the dermis and around dorsal root ganglion neurons, thereby being implicated in the generation of pain sensation."[9] Growth factors may be important in this disorder as listed by : (1) endogenous growth factors promote survival and health of neurons, (2) expression levels of growth factors are altered in diabetic neuropathy and peripheral neuron injury, and (3) growth factors induce neuronal regeneration in in vitro and in vivo models of diabetic injury".[10]

Neurotrophic factors can promote the survival or growth of different neuronal populations which was demonstrated by in-vitro evidence[11] through their paracrine and autocrine actions.[12] Studies with NGF, NT-3, IGF-I and IGF-II both in vitro and in animal models of neuropathies (including DPN) suggest that these factors ameliorate nerve degeneration.[13,14] Recombinant human nerve growth factor (rhNGF) was extensively studied and reported for its efficacy in animal studies of DPN.[15]

Although existing evidence suggested alterations in nerve growth factor levels in experimental DPN, it is yet to be established whether observed growth factor deficiencies were due to decreased synthesis, or functional, e.g. an inability to bind to their receptor, and/or abnormalities in nerve transport and processing.[16]

References

1. Apfel SC. Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold? *Int Rev Neurobiol.* 2002; 50: 393-413.
2. Apfel SC. Neurotrophic factors in peripheral neuropathies: therapeutic implications. *Brain Pathol.* 1999b; 9(2): 393-413.
3. Apfel SC. Neurotrophic factors in peripheral neuropathies: therapeutic implications. *Brain Pathol.* 1999d; 9(2): 393-413.
4. Brewster WJ, Fernyhough P, Diemel LT, Mohiuddin L, Tomlinson DR. Diabetic neuropathy, nerve growth factor and other neurotrophic factors. *Trends Neurosci.* 1994; 17(8): 321-5.
5. Dobrowsky RT, Rouen S, Yu C. Altered neurotrophism in diabetic neuropathy: spelunking the caves of peripheral nerve. *J Pharmacol Exp Ther.* 2005; 313(2): 485-91.
6. Zochodne DW. Neurotrophins and other growth factors in diabetic neuropathy. *Semin Neurol.* 1996; 16(2): 153-61.
7. Apfel SC, Kessler JA. Neurotrophic factors in the therapy of peripheral neuropathy. *Baillieres Clin Neurol.* 1995; 4(3): 593-606.
8. Tomlinson DR, Fernyhough P, Diemel LT. Role of neurotrophins in diabetic neuropathy and treatment with nerve growth factors. *Diabetes.* 1997; 46(Suppl 2): S43-9.
9. Yasuda H, Terada M, Maeda K, Kogawa S, Sanada M, Haneda M, *et al.* Diabetic neuropathy and nerve regeneration. *Prog Neurobiol.* 2003; 69(4): 229-85.
10. Leinninger GM, Vincent AM, Feldman EL. The role of growth factors in diabetic peripheral neuropathy. *J Peripher Nerv Syst.* 2004; 9(1): 26-53.
11. McMahon SB, Priestley JV. Peripheral neuropathies and neurotrophic factors: animal models and clinical perspectives. *Curr Opin Neurobiol.* 1995; 5(5): 616-24.

12. Davies AM. Paracrine and autocrine actions of neurotrophic factors. *Neurochem Res.* 1996; 21(7): 749-53.
13. Apfel SC. Neurotrophic factors and diabetic peripheral neuropathy. *Eur Neurol.* 1999c; 41(Suppl 1): 27-34.
14. Calcutt NA, Jolivalt CG, Fernyhough P. Growth factors as therapeutics for diabetic neuropathy.*Curr Drug Targets.* 2008; 9(1): 47-59.
15. Apfel SC. Neurotrophic factors in the therapy of diabetic neuropathy. *Am J Med.* 1999a; 107(2B): 34S-42S.
16. Pittenger G, Vinik A. Nerve growth factor and diabetic neuropathy. *Exp Diabesity Res.* 2003; 4(4): 271-85.