Indian Journal of Genetics and Molecular Research
Volume 2 Number 2, July - December 2013

Vascular Endothelial Growth Factors in Diabetic Peripheral Neuropathy: Neuropathogenetic or Neuroprotective?

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Abstract

Vascular endothelial growth factor (VEGF) is a growth factor gene primarily responsible for angiogenesis, and is now hypothesized to play a role in neurodegeneration and neuroregeneration in peripheral neuropathies. The aim of this short communication was to highlight the role of VEGF in diabetic peripheral neuropathy (DPN). There is limited but sufficient evidence for role of VEGF in pathogenesis, and abnormal VEGF levels were found on assessment of DPN. Treatments with VEGF had reversed electrophysiological measures in DPN and also other treatments such as Frequency Modulated Electrical Muscle Stimulation (FREMS) was shown to increase VEGF levels, thus reiterating the diagnostic, therapeutic and prognostic role of VEGF in DPN.

Keywords: Neurotrophic factors; VEGF; Vasa nervorum; Diabetic neuropathy.

Vascular endothelial growth factor (VEGF) is a growth factor gene primarily responsible for angiogenesis, and is now hypothesized to play a role in neurodegeneration and neuroregeneration in peripheral neuropathies. The aim of this short communication was to highlight the role of VEGF in diabetic peripheral neuropathy (DPN).

Altered expression of VEGF was reported by three studies: Quattrini *et al* assessed the expression of VEGF and intra-epidermal nerve fiber density (IENFD) in skin biopsy samples from 53 diabetic patients and 12 nondiabetic control subjects and the intensity of staining for epidermal VEGF-A was found to be reduced in diabetic patients compared with control subjects [1]; Samii *et al* found that "functional alteration of peripheral nerves caused up-regulation of VEGF in Schwann cells and neurons. With functional restitution of nervous tissue, i.e. under insulin and/or NGF treatment VEGF expression decreases significantly. Additionally, NGF may stimulate VEGF in normal controls."[2]

Zakareia evaluated the electro-physiological changes, blood flow index, vascular endothelial growth factor (VEGF), soluble fatty acid synthase (s-FAS), and intercellular adhesion molecule (I-CAM) in 30 controls (group I), 30 diabetics type II without complications (group II), and 30 with peripheral neuropathy (group III). "There was a significant increase of plasma VEGF, s-FAS, and ICAM all in group III compared to groups I and II. The results revealed that VEGF and s-FAS are good predictors for median nerve motor conduction velocity, also VEGF is a good predictor of sural nerve sensory conduction velocity in diabetic neuropathy."[3]

VEGF was used to prevent DPN as demonstrated by Chattopadhyay *et al* who examined the utility of herpes simplex virus (HSV) vector-mediated gene transfer of vascular endothelial growth factor (VEGF) in a mouse model of diabetic neuropathy was found to preserve autonomic function (measured by pilocarpine-induced sweating), and prevent the loss of nerve fibers in the skin and reduce neuropeptide calcitonin gene-

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related peptide and substance P in DRG neurons of the diabetic mice. Kessler[5] also emphasized that VEGF gene transfer could be used for prevention and treatment of diabetic polyneuropathy.[4]

VEGF treatment in DPN was reported by Ropper *et al* who conducted a randomized, blinded trial of intramuscular gene transfer using plasmid vascular endothelial growth factor (VEGF) to treat 50 diabetic polyneuropathy patients who were randomized to receive a VEGF-to-placebo ratio of 3:1 Intramuscular plasmid VEGF gene transfer was found to improve diabetic neuropathic symptoms (mean symptom score, sensory loss, VAS score) for efficacy but with serious adverse events.[6]

Zakareia *et al* opined, "the rise of VEGF in diabetic neuropathy may be protective to preserve the nerve blood flow, the significant rise of s-FAS may be causative in advancement of neuropathy, I-CAM high levels suggest its leading role in interaction between endothelium, blood elements, and peripheral nerves."[3]

Other treatments such as Frequency Modulated Electrical Muscle Stimulation (FREMS) was reported by Bevilacqua *et al*[7] who compared the effects of Frequency Modulated Electrical Muscle Stimulation (FREMS) vs transcutaneous electrical nerve stimulation (TENS) on the release of vascular endothelial growth factor (VEGF) in 10 Type 2 diabetic and in 10 non-diabetic subjects and found significant rise in plasma VEGF during FREMS in both non-diabetic and diabetic subjects compared to that of TENS application.

There was limited but sufficient evidence for role of VEGF in pathogenesis, and abnormal VEGF levels were found on assessment of DPN. Treatments with VEGF had reversed electrophysiological measures in DPN and also other treatments such as Frequency Modulated Electrical Muscle Stimulation (FREMS) was shown to increase VEGF levels, thus reiterating the diagnostic, therapeutic and prognostic role of VEGF in DPN.

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