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Molecular Basis of Diabetic Peripheral Neuropathy: Role of Oxidative Stress

Nisha Rani Jamwal, Kumar Senthil P.*, Adhikari Prabha, Jeganathan PS*****

Abstract

It is well known that hyperglycemia is the predominant manifestation in diabetes mellitus, and the most common complication of DM is diabetic peripheral neuropathy (DPN). The aim of this short communication was to provide an insightful overview of the molecular basis of DPN by assimilating evidence on the role of oxidative stress. Existing evidence indicated that oxidative stress might be a final common pathway in the development of diabetic neuropathy, and that antioxidants could prevent or reverse hyperglycemia-induced nerve dysfunction. The effects of antioxidants were hypothesized to be mediated by correction of nutritive blood flow, and endoneurial oxidative state; and antioxidant drugs such as alpha-lipoic acid and vitamin E were therapeutically indicated.

Keywords: Molecular endocrinology; Molecular neurology; Diabetic neuropathy; Oxidative stress.

It is well known that hyperglycemia is the predominant manifestation in diabetes mellitus, and the most common complication of DM is diabetic peripheral neuropathy (DPN). The aim of this short communication was to provide an insightful overview of the molecular basis of DPN by assimilating evidence on the role of oxidative stress.

Figueroa-Romero *et al*[1] explained that "excess glucose overloads the electron transport chain, leading to the production of superoxides and subsequent mitochondrial and cytosolic oxidative stress. These changes include the production of advanced glycation end products, alterations in the sorbitol, hexosamine and protein kinase C pathways and activation of poly-ADP ribose polymerase."

Pop-Busui *et al*[2] reviewed the impact of hyperglycemia-induced oxidative stress in the development of diabetes-related neural dysfunction and explained, "Oxidative stress occurs when the balance between the production of reactive oxygen species (ROS) and the ability of cells or tissues to detoxify the free radicals produced during metabolic activity is tilted in the favor of the former. Although hyperglycemia plays a key role in inducing oxidative stress in the diabetic nerve, the contribution of other factors, such as endoneurial hypoxia, transition metal imbalances, and hyperlipidemia have been also suggested. The possible sources for the overproduction of ROS in diabetes are widespread and include enzymatic pathways, auto-oxidation of glucose, and mitochondrial superoxide production."

Greene *et al*[3] established that"glucose-derived oxidative stressplayed a central role, linking together with the aldose reductase and glycation pathways, vascular dysfunction, and impaired neurotrophic support. Vincent *et al* (2004) in their review explored the concept that diabetes overloaded glucose metabolic

Author's Affiliation: Post-graduate Student,*Professor & Principal, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation (Maharishi Markandeshwar University), Mullana – Amabala, Haryana,India. **Professor, Dept. of Medicine, ***Professor, Dept. of Physiology, Kasturba Medical College (Manipal University), Mangalore, Karnataka, India.

Corresponding Author: Senthil P. Kumar, Professor & Principal, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation (Maharishi Markandeshwar University), Mullana– Ambala, Haryana, India.

E-mail: senthilparamasivamkumar@gmail.com

pathways, resulting in excess free radical production and oxidative stress. Proteins that were damaged by oxidative stress in turn bear decreased biological activity leading to loss of energy metabolism, cell signalling, transport, and, ultimately, to programmed cell death or apoptosis.

Negi *et al*[4] postulated that excessive production of reactive oxygen species was a key component in the development and progression of diabetic neuropathy. Therapeutic strategies utilizing a more targeted approach like focusing on Nrf2 (a transcription factor modulating oxidative stress) might provide an enthralling avenue to optimize neuroprotection in diabetes and diabetic neuropathy.

Nazýroðlu *et al*[5] reviewed the role of Ca(2+) signalling through cation channels and oxidative stress on diabetic neuropathic pain in sensory neurons, and found "the polyol pathway, advanced glycation end products, oxidative stress, protein kinase C activation, neurotrophism, and hypoxiaand deficits in insulin trigger alterations of sensory neurone phenotype."

van Dam[6] emphasized that oxidative stress might be a final common pathway in the development of diabetic neuropathy, and that antioxidants could prevent or reverse hyperglycaemia-induced nerve dysfunction. The effects of antioxidants were hypothesized to be mediated by correction of nutritive blood flow, and endoneurial oxidative state; and antioxidant drugs such as alpha-lipoic acid and vitamin E were therapeutically indicated.

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