

Molecular Basis of Diabetic Peripheral Neuropathy: Role of Oxidative Stress

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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.

Figuroa-Romero et al [1] explained that "excess glucose overloads the electron transport chain, leading to the production of super-oxides 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 stress played 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 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 signaling, 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)

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might provide an enthralling avenue to optimize neuroprotection in diabetes and diabetic neuropathy.

Nazýrođlu et al [5] reviewed the role of Ca (2+) signaling 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 hypoxia and 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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