Mitochondrial Function and Dysfunction in Diabetic Peripheral Neuropathy: An Updated Overview of Studies to Implicate Physiological Basis of Neuropathological Condition

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Abstract

This short communication article was aimed to provide an evidence-informed overview and a scoping review of the role of mitochondrial function/dysfunction in diabetic peripheral neuropathy (DPN). From the reviewed studies, it is apparently evident that mitochondria played a comprehensive role not only in predisposing oxidative stress but also in programmed cell death or apoptosis in DPN.

Keywords: Mitochondrial function; Oxidative stress; Pathophysiology; Diabetic neuropathy.

This short communication article was aimed to provide an evidence-informed overview and a scoping review of the role of mitochondrial function/dysfunction in diabetic peripheral neuropathy (DPN).

4-Hydroxy-2-nonenal induces mitochondrial dysfunction: Akude *et al*[1] tested the hypothesis that exposure of cultured adult rat sensory neurons to 4-hydroxy-2-nonenal (4-HNE) would result in the formation of amino acid adducts on mitochondrial proteins and that this process would be associated with impaired mitochondrial function and axonal regeneration. 4-HNE was shown to induce formation of protein adducts on cytoskel *et al* and mitochondrial proteins, and impaired axon regeneration by approximately 50% at 3 micro M while initiating formation of aberrant axonal structures and caused the accumulation of mitochondria in these dystrophic structures.

Chowdhury *et al*[2] summarized the major features of mitochondrial dysfunction in neurons and Schwann cells in human diabetic patients and in experimental animal models (primarily exhibiting type 1 diabetes) and emphasized, "hyperglycemia in diabetes triggers nutrient excess in neurons that, in turn, mediates a phenotypic change in mitochondrial biology through alteration of the AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor ã coactivator-1á (PGC-1á) signaling axis. This vital energy sensing metabolic pathway modulates mitochondrial function, biogenesis and regeneration.

Fernyhough et al[3] summarized the nature of sensory and autonomic nerve dysfunction in diabetes-induced nerve degeneration mediated by alterations in mitochondrial ultra structure, physiology and trafficking. A reduction in electron

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transport chain capability might predispose mitochondria to generate elevated reactive oxygen species (ROS), which would deleteriously alter the bio-energetic status of neurons.

Fernyhough *et al*[4] demonstrated that insulin and neurotrophin-3 (NT-3) modulate mitochondrial membrane potential in cultured adult sensory neurons and Diabetes caused a significant loss of mitochondrial membrane potential in all sub-populations of sensory neurons which was treated with insulin or NT-3. Their results showed that in adult sensory neurons, treatment with insulin could elevate the input of reducing equivalents into the mitochondrial electron transport chain, which lead to greater mitochondrial membrane polarization and enhanced ATP synthesis.

Adenosine monophosphate-activated protein kinase: Roy Chowdhury *et al*[5] assessed the deficits in adenosine monophosphate-activated protein kinase/ peroxisome proliferator-activated receptor ã coactivator-1á (PGC-1á) signalling in sensory neurons in rodent models of type 1 and type 2 diabetes. The study had following findings: "Phosphorylation and expression of adenosine monophosphate-activated protein kinase/PGC-1á and mitochondrial respiratory chain complex proteins were down regulated in dorsal root ganglia of both streptozotocin-diabetic rats and db/db mice. The bioenergetics profile (maximal oxygen consumption rate, coupling efficiency, respiratory control ratio and spare respiratory capacity) was aberrant in cultured sensory neurons from streptozotocin-diabetic rats and was corrected by resveratrol treatment."

Ciliary neurotrophic factor: Salehet al[6] tested the hypothesis that Ciliary neurotrophic factor (CNTF) protects sensory neuron function during diabetes through normalization of impaired mitochondrial bioenergetics. Neurite outgrowth of sensory neurons derived from streptozotocin (STZ)-induced diabetic rats was reduced compared to neurons from control rats and exposure to CNTF for 24 h enhanced neurite outgrowth. The authors proposed that the ability of CNTF to enhance axon regeneration and protect peripheral nerve from structural and functional indices of diabetic peripheral neuropathy was associated with targeting of mitochondrial function, and in part via NF-êB activation, and improvement of cellular bioenergetics.

Srinivasan *et al*[7] opined that diabetic sensory neuropathy was associated with activation of apoptosis and concomitant mitochondrial dysfunction. These findings were confirmed by the presence of basal mitochondrial membrane potential (deltapsi) being more positive in DRG neurons from diabetic rats.

Chaperones: Urban *et al*[8] proposed that modulating the activity and expression of heat shock proteins (Hsp) might be of benefit in treating DPN. KU-32 was found to improve physiological and morphologic markers of degenerative neuropathy and drug efficacy might be related to enhanced mitochondrial bioenergetics in sensory neurons.

Vincent *et al*[9] reported a greater number of mitochondria in both myelinated and unmyelinated dorsal root axons in a well-established model of murine diabetic neuropathy by examining mitochondrial biogenesis and fission in response to hyperglycemia in the neurites of cultured DRG neurons. The study demonstrated overall mitochondrial biogenesis via increases in mitochondrial transcription factors and increases in mitochondrial DNA in both DRG neurons and axons. The authors concluded that "during acute hyperglycemia, mitochondrial fission was a prominent response, and excessive mitochondrial fission might result in dysregulation of energy production, activation of caspase 3, and subsequent DRG neuron injury. During more prolonged hyperglycemia, there was evidence of compensatory mitochondrial biogenesis in axons."

From the reviewed studies, it was apparently evident that mitochondria played a comprehensive role not only in predisposing oxidative stress but also in programmed cell death or apoptosis in DPN.

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