Neurobiology of Disease 51 (2013) 56–65

Contents lists available at SciVerse ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

The role of aberrant mitochondrial bioenergetics in diabetic neuropathy

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ARTICLE INFO

Article history:
Received 7 November 2011
Revised 22 February 2012
Accepted 1 March 2012
Available online 9 March 2012

Keywords:
AMP-activated protein kinase
Axonal plasticity
Axonopathy
Diabetes
Dorsal root ganglia
Mitochondrial depolarization
Nutrient excess
Respiration
Respiratory chain
Schwann cell

ABSTRACT

Diabetic neuropathy is a neurological complication of diabetes that causes significant morbidity and, because of the obesity-driven rise in incidence of type 2 diabetes, is becoming a major international health problem. Mitochondrial phenotype is abnormal in sensory neurons in diabetes and may contribute to the etiology of diabetic neuropathy where a distal dying-back neurodegenerative process is a key component contributing to fiber loss. This review summarizes 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). This article attempts to relate these findings to the development of critical neuropathological hallmarks of the disease. Recent work reveals that 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 γ coactivator-1α (PGC-1α) signaling axis. This vital energy sensing metabolic pathway modulates mitochondrial function, biogenesis and regeneration. The bioenergetic phenotype of mitochondria in diabetic neurons is aberrant due to deleterious alterations in expression and activity of respiratory chain components as a direct consequence of abnormal AMPK/PGC-1α signaling. Utilization of innovative respirometry equipment to analyze mitochondrial function of cultured adult sensory neurons from diabetic rodents shows that the outcome for cellular bioenergetics is a reduced adaptability to fluctuations in ATP demand. The diabetes-induced maladaptive process is hypothesized to result in exhaustion of the ATP supply in the distal nerve compartment and induction of nerve fiber dissolution. The role of mitochondrial dysfunction in the etiology of diabetic neuropathy is compared with other types of neuropathy with a distal dying-back pathology such as Friedreich ataxia, Charcot–Marie–Tooth disease type 2 and human immunodeficiency virus-associated distal-symmetric neuropathy.

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.nbd.2012.03.016

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Introduction

This review will focus on aspects of mitochondrial dysfunction in neurons and Schwann cells in the setting of diabetes and diabetic neuropathy. Diabetic neuropathy, a common neurological complication of diabetes, exhibits a distal dying-back process of nerve fiber degeneration that is seen in other neuropathic diseases such as Friedreich ataxia, Charcot–Marie–Tooth disease type 2 (CMT2; an axonal form) and human immunodeficiency virus-associated distal-symmetric neuropathy (HIV-DSP). Importantly, it is now clear that all of these diseases incorporate a component involving mitochondrial dysfunction. In other neuropathies with a dying-back type axonopathy, such as leprosy and myriad chemical-induced neuropathies, the specific role of mitochondrial dysfunction in etiology is less well characterized. However, the reader is referred to work by Bennett et al. with regard to mitochondrial dysfunction in chemotherapy (taxol or oxaliplatin)-induced peripheral neuropathy (Bennett et al., 2011; Xiao et al., 2011; Zheng et al., 2011). This review will concentrate on newly characterized features of mitochondrial physiology that are abnormal in diabetic neuropathy and will take an axon-centric view but will also consider Schwann cell involvement, although data in this area are lacking. For background information the reader is directed toward recent exhaustive reviews covering broad aspects of the putative etiologies underpinning neuropathy and the diabetic complications (Calcutt et al., 2009a; Sugimoto et al., 2008; Tomlinson and Gardiner, 2008) and more specifically the role of mitochondrial dysfunction in the development of diabetic complications (Sivitz and Yorek, 2010). Dyslipidemia has also been introduced as an etiological factor contributing to diabetic neuropathy (Vincent et al., 2009), although supporting experimental data is limited and awaits verification. For more specific coverage of mitochondrial abnormalities in diabetic neuropathy, with a focus on metabolic pathway involvement and alterations in organelle biogenesis and trafficking, the reader is referred to the following articles (Chowdhury et al., 2011; Fernyhough et al., 2010).

Clinical impact of diabetic neuropathy

The World Health Organization (WHO) predicts that by 2025 there will be 300 million people with diabetes. In North America 19 million people currently have diabetes with an incidence of 6% and rising. Of those, approximately 90–95% has non-insulin-dependent diabetes mellitus (type 2 diabetes) and 5–10% has insulin-dependent diabetes mellitus (type 1 diabetes). In the USA approximately US$25 billion per annum is spent on the treatment of diabetic complications that include retinopathy, nephropathy, heart disease and neuropathy. In 1998 approximately US$15 billion of the health service expenditure was associated with neurological complications (sensory and autonomic neuropathy and blindness). The incidence of symmetrical polyneuropathy, the most common presentation of neuropathy, in diabetic patients can be 50% or higher and leads to incapacitating pain, sensory loss, foot ulceration (up to 2 million Americans have this complaint), infection, gangrene and poor wound healing. Lower extremity amputation often follows and accounts for approximately 80,000 cases each year in the USA. There is no effective therapy for diabetic symmetrical polyneuropathy or any form of neuropathy, only palliative treatment is available at the present time. These alarming figures are predicted to rise by approximately 5-fold over the next 10 years due to the epidemic in obesity and the associated increase in incidence and earlier time of onset of type 2 diabetes (Fernyhough et al., 2010).

Nerve pathology in diabetic neuropathy

Symmetrical polyneuropathy in types 1 and 2 diabetic patients is associated with a reduction in motor and sensory nerve conduction velocity and appearance of structural changes in the peripheral nerves including endoneurial microangiopathy (Malik et al., 2005), abnormal Schwann cell pathology (Kalichman et al., 1998), axonal degeneration, paranodal demyelination, and loss of myelinated and unmyelinated fibers (Said, 2007; Yagihashi, 1996); the latter due to a dying-back of distal axons that presents clinically as reduced epidermal nerve fiber density (Ebenezer et al., 2011; Kennedy et al., 1996; Quattrini et al., 2007). Neurodegeneration is most profound in the longest axons of neurons (Said, 2007), and defective axon regeneration impedes tissue re-innervation (Ebenezer et al., 2011; Polydefkis et al., 2004). These clinical endpoints as well as indications of pain are observed in animal models with diabetic neuropathy, with demyelination being the only pathological sign that is not present reproducibly (Beiswenger et al., 2008; Christianson et al., 2003, 2007; Francis et al., 2009; Jolivalt et al., 2008; Mizisin et al., 2007). While demyelination is not present in some animal models, in long term streptozotocin (STZ)-induced diabetic mice (a model of type 1 diabetes) there was evidence of myelin thinning (Kennedy and Zochodne, 2005a). Furthermore, a recent gene array study of nerve in *db*/*db* diabetic mice (a model of type 2 diabetes) revealed a range of deficits in myelin protein-associated gene expression (Pande et al., 2011). Complementary studies using co-cultures of sensory neurons and Schwann cells and the examination of STZ-diabetic mice suggest demyelination, and the attendant deficits in sensory function may be associated with hyperglycemia-induced aberrant caveolin and neuregulin/erbB2 signaling (Dobrowsky et al., 2005; McGuire et al., 2009; Yu et al., 2008).

Shrinkage of perikaryal volume occurs within the dorsal root ganglia (DRG) in animal models of diabetes, however, there is no molecular signature or sign of apoptosis-dependent loss of sensory neuron perikarya in diabetic humans or animals (Burnand et al., 2004; Cheng and Zochodne, 2003; Kamiya et al., 2006; Schmidt et al., 1997; Sidenius and Jakobsen, 1980). Nevertheless, loss of small neurons, through a yet to be defined mechanism, does occur in mouse and rat models (Jiang et al., 2004; Kamiya et al., 2006; Kennedy and Zochodne, 2005a). The distal dying-back and formation of axonal dystrophy (with swellings) of axons are critical pathological features (Kennedy et al., 1996; Lauria et al., 2003; Polydefkis et al., 2004; Schmidt, 2002; Schmidt et al., 1981; Zherebitskaya et al., 2009) and mimic axonal pruning and degeneration observed in the CNS and PNS in other pathological states (Nja and Purves, 1978; Verkhratsky and Fernyhough, 2008).

Mitochondrial ultrastructure in diabetic neuropathy

During peripheral nerve degeneration in diabetes in both humans and animal models subtle changes in mitochondrial number and size have been described in Schwann cells of myelinated and non-