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Review

Pathogenesis of diabetic neuropathy: Focus on neurovascular mechanisms

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ABSTRACT

Neuropathies of the peripheral and autonomic nervous systems affect up to half of all people with diabetes, and are major risk factors for foot ulceration and amputation. The aetiology is multifactorial: metabolic changes in diabetes may directly affect neural tissue, but importantly, neurodegenerative changes are precipitated by compromised nerve vascular supply. Experiments in animal models of diabetic neuropathy suggest that similar metabolic sequelae affect neurons and vasa nervorum endothelium. These include elevated polyol pathway activity, oxidative stress, the formation of advanced glycation and lipoxidation end products, and various pro-inflammatory changes such as elevated protein kinase C, nuclear factor κB and p38 mitogen activated protein kinase signalling. These mechanisms do not work in isolation but strongly interact in a mutually facilitatory fashion. Nitrosative stress and the induction of the enzyme poly (ADP-ribose) polymerase form one important link between physiological stressors such as reactive oxygen species and the pro-inflammatory mechanisms. Recently, evidence points to endoplasmic stress and the unfolded protein response as forming another crucial link. This review focuses on the aetiopathogenesis of neurovascular changes in diabetic neuropathy, elucidated in animal studies, and on putative therapeutic targets the majority of which have yet to be tested for efficacy in clinical trials.

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1. Introduction

Peripheral neuropathies affect up to 50% of people with diabetes. The diffuse neuropathies, distal symmetrical sensori-motor polyneuropathy (DPN) and autonomic neuropathy (DAN) are common. They constitute major risk factors for foot ulceration and amputation (Boulton, 2005). All nerve fibre types are adversely affected by diabetes; autonomic, motor and sensory, myelinated and unmyelinated.

DPN gives rise to a "stocking-glove" pattern of sensory loss progressing proximally with increasing diabetes duration. DAN causes dysfunction of major organ systems including cardiac, gastrointestinal and urogenital (Vinik et al., 2003). Both DPN and

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DAN markedly reduce quality of life and increase mortality. To date no satisfactory treatment targeting the causes of neuropathy exists except for good metabolic control, which slows but does not prevent progression (Cameron et al., 2001).

The aetiologies of DPN and DAN are multi-factorial. Studies by the Eurodiab group on type 1 diabetes complications showed that in addition to glycaemic control and duration of diabetes, conventional markers of macro- and micro-vascular disease are strongly associated with DPN (Tesfaye et al., 2005). Similar correlations have been observed for DPN in type 2 diabetes (Papanus and Ziegler, 2012; Ziegler et al., 2008) and for cardiac DAN (Witte et al., 2005). Thus, while the metabolic insult of diabetes may directly affect neural tissue, it is likely that neurodegenerative changes are precipitated by compromised nerve vascular supply. This is in line with earlier work that showed pathological changes in vasa nervorum epi/perineurial and endoneurial vessels (Fagerberg, 1957) and established good correlations between vascular parameters, nerve structural damage and measures of function such as nerve conduction velocity, vibration perception thresholds and thermal discrimination (Giannini and Dyck, 1995; Malik et al., 1989, 1994). These vascular changes occur early, when nerve pathology and neuropathy is minimal (Malik et al., 2005). Physiological measurements of sural nerve oxygen tension and blood flow in patients show that the endoneurium is hypo-perfused and hypoxic with diabetes, and that this is exacerbated in subjects with neuropathy (Ibrahim et al., 1999; Newrick et al., 1986; Tesfaye et al., 1993). An important contributory factor, revealed by photography of epi/perineurial vessels, was an increase of arterio-venous shunting in patients with neuropathy, bypassing the nutritive endoneurial circulation (Tesfaye et al., 1993). Other morphological studies showed denervation of perineurial vessels, suggesting that DAN could potentially contribute to the impaired control of nerve perfusion in diabetes (Beggs et al., 1992). Whether the resultant hypoxic stress on nerve fibres is sufficient to account for diabetic neuropathy or whether it acts in concert with direct metabolic stress on nerve fibres resulting from the diabetic milieu cannot be answered by the limited number of investigations carried out to date in patients. However, data from animal models provides further insight into the pathogenetic mechanisms underlying DPN, and pharmacological intervention studies have revealed numerous potential therapeutic targets, a small number of which have advanced to clinical trials.The aim of this review is to provide an update on the putative mechanisms leading to DPN/DAN in diabetes mellitus, with a focus on neurovascular dysfunction.

2. Vasa nervorum changes and endoneurial ischaemia in experimental diabetes

It is generally agreed that nerve blood flow is reduced by diabetes. In chemically-induced animal models such as the streptozotocin (STZ)-treated rat, this occurs within the first few days of diabetes induction, preceding changes in nerve electrophysiology such as reduced conduction velocity (Cameron et al., 1991; Coppey et al., 2000; Wright and Nukada, 1994). The perfusion deficit causes endoneurial hypoxia sufficient to compromise nerve function and initiate neurodegenerative processes (Tuck et al., 1984). Findings from initial research in the STZ-induced rat model of type 1 diabetes have been extended to other models including the BB-Wor type 1 model (Stevens et al., 2004); the type 2 models Zucker diabetic fatty rat (Oltman et al., 2009), Otsuka Long-Evans Tokushima fatty rats (Nakamura et al., 2001) and high fat-fed low-dose STZ-induced diabetic rats (Davidson et al., 2011) and even for diet-induced obese rats (Davidson et al., 2010). Impaired sciatic nerve blood flow and vascularity has also been demonstrated in STZ-diabetic mice (type 1) and db/db mice (type 2) (Himeno et al., 2011; Masaaki et al., 2005). This effect is not restricted to peripheral nerve trunks, but is also seen in autonomic ganglia, dorsal root ganglia (DRG), and even centrally in some brain structures such as the hippocampus (Cameron and Cotter, 2001a; Manschot et al., 2003; Sasaki et al., 1997).

A fundamental reason for reduced nerve tissue perfusion is that diabetes produces an endotheliopathy in vasa nervorum, paralleling that found in several other vascular beds. Metabolic alterations cause reductions in endothelial output/effects of the major vasodilators, nitric oxide (NO) and endothelium-derived hyperpolarising factor (EDHF) (Coppey et al., 2003; Kihara and Low, 1995; Maxfield et al., 1997). This reduces vasodilation and potentiates vasoconstriction by agents that may be elevated in diabetes, such as angiotensin II, endothelin 1 and sympathetic tone (Cameron et al., 2001).

Vasodilator treatment experiments have the potential to provide some information on the relative importance of vascular versus neural pathophysiology in DPN, as well as testing a pragmatic putative therapeutic approach. A considerable number of such studies have been undertaken, using a variety of agents such as angiotensin converting enzyme inhibitors, calcium channel blockers, endothelin-1 receptor antagonists, and alpha1 adrenoceptor blockers. Most investigations have used the STZ-diabetic rat model, and the main findings point to improvements in nerve electrophysiology (motor and sensory conduction velocity) which correlate strongly with the degree of correction of diabetic endoneurial perfusion deficits (see Cameron et al., 2001 for a review). Good correlations have also been established between nerve blood flow and the degree of thermal hyperalgesia or tactile allodynia (Cameron and Cotter, 2007). Angiotensin converting enzyme inhibition has also been shown to protect against the loss of intraepidemal nerve fibres in a type 2 diabetes rat model (Davidson et al., 2012). In terms of clinical trials, angiotensin converting enzyme inhibition produced some modest improvements in DPN and cardiac DAN (Kontopoulos et al., 1997; Malik et al., 1998). Thus, while it is clear that nerve blood flow deficits make an important contribution to the pathogenesis of diabetic neuropathy, the challenge is to identify the metabolic alterations in diabetes that cause neural and vascular changes, and the disruptions they promote in cellular signalling cascades. These then can form a basis for potential therapeutic intervention to augment the beneficial effects of good diabetic and cardiovascular control. Considerable scientific progress has been made over the last decade or so in this regard.

3. Metabolic alterations in diabetes and the pathogenesis of neuropathy

Some of the major metabolic changes in diabetes thought to contribute to DPN and DAN are schematised in Fig. 1. These include elevated polyol pathway activity, oxidative stress, the formation of advanced glycation end products, and various proinflammatory changes such as elevated nuclear factor κB (NFκB) and p38 mitogen activated protein kinase (MAPK) signalling. These mechanisms do not work in isolation but strongly interact in a mutually facilitatory fashion. Other mechanisms include increased poly (ADP-ribose) polymerase (PARP) activity, increased lipoxygenase activity, and elevated Na^+/H^+ exchanger-1 action. Recently it has been found that activation of endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) may be key players in diabetic complications, including neuropathy (Cameron, 2013; Lupachyk et al., 2013).

3.1. Polyol pathway

The polyol pathway is present in many tissues including peripheral nerve and blood vessels. Glucose is converted to

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