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Review

Diabetes and the peripheral nerve☆

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ABSTRACT

Diabetes-induced damage to peripheral nerve culminates in development of peripheral diabetic neuropathy (PDN), one of the most devastating complications of diabetes mellitus and a leading cause of foot amputation. The pathogenesis of PDN occurs as a consequence of complex interactions among multiple hyperglycemia-initiated mechanisms, impaired insulin signaling, inflammation, hypertension, and disturbances of fatty acid and lipid metabolism. This review describes experimental new findings in animal and cell culture models as well as clinical data suggesting the importance of 1) previously established hyperglycemia-initiated mechanisms such as increased aldose reductase activity, non-enzymatic glycation/glycooxidation, activation of protein kinase C, 2) oxidative–nitrosative stress and poly(ADP-ribose) polymerase activation; 3) mitogen-activated protein kinase and cyclooxygenase-2 activation, impaired Ca^{++} homeostasis and signaling, and several other mechanisms, in PDN.

1. Introduction

Diabetic distal symmetric sensorimotor polyneuropathy affects at least 50% of diabetic patients, and is the leading cause of foot amputation [1]. Two largest clinical trials in subjects with Type 1 and Type 2 diabetes i.e., Diabetes Control and Complication Trial (DCCT) and UK Prospective Diabetes Study (UKPDS), indicate that intensive therapy and improved blood glucose control reduce incidence and slow progression of peripheral diabetic neuropathy (PDN) thus implicating hyperglycemia as a leading causative factor [1–3]. A number of mechanisms have been proposed to link chronic hyperglycemia to diabetes-induced deficits in motor and sensory nerve conduction velocities (MNCV and SNCV) and small fiber sensory neuropathy. The vascular concept of PDN implies that diabetes-induced endothelial dysfunction with resulting decrease in nerve blood flow (NBF), vascular reactivity, and endoneurial hypoxia has a key role in functional and morphological changes in the diabetic nerve [4]. Endothelial changes in *vasa nervorum* have been attributed to multiple mechanisms including increased aldose reductase (AR) activity, non-enzymatic glycation and glycoxidation, activation of protein kinase C, oxidative–nitrosative stress, changes in arachidonic acid and prostaglandin metabolism [4], and, recently, decreased expression of the vanilloid receptor 1 in vasa nervorum [5], increased production of angiotensin (AT) II and activation of the AT1-receptor [6], activation of poly(ADP-ribose) polymerase-1 (PARP) [7], nuclear factor-κB (NF-κB, [8]), cyclooxygenase-2 (COX-2) [9], and others. The neurochemical concept of PDN suggests the importance of similar mechanisms in the *neural* elements of PNS i.e., Schwann cells, spinal cord oligodendrocytes, and dorsal root ganglion neurons. Other pathobiochemical mechanisms such as 1) metabolic abnormalities i.e., downregulation of Na^+/K^+ ATP-ase activity [10], "pseudohypoxia" — an increase in free cytosolic NADH/NAD^+ ratio putitatively linked to increased conversion of sorbitol to fructose by sorbitol dehydrogenase [11], changes in fatty acid and phospholipid metabolism [12], 2) impaired neurotrophic support [13,14], 3) changes in signal transduction [15], and 4) dorsal root ganglion (DRG) and Schwann cell mitochondrial dysfunction and premature apoptosis [16,17], have also been invoked. The present review of the recent findings has two major objectives i.e. 1) to evaluate new experimental evidence that supports or disproves previously formulated concepts of the pathogenesis of PDN, and 2) to characterize newly discovered mechanisms.

2. Role for aldose reductase

The sorbitol pathway of glucose metabolism consists of two reactions. First, glucose is reduced to its sugar alcohol sorbitol by NADPH-dependent AR. Then, sorbitol is oxidized to fructose by NAD-

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dependent sorbitol dehydrogenase (SDH). Sorbitol accumulation in the peripheral nerve is well documented in STZ-diabetic rodents [18,19] and has recently been described in leptin-deficient (*ob*/*ob*) mice [20]. Interestingly and excitingly, increased sorbitol pathway activity manifest by sciatic nerve sorbitol and fructose accumulation is also clearly manifest in the high fat diet (HFD) model of prediabetic neuropathy characterized by impaired glucose tolerance, increased serum nonesterified fatty acid concentrations and insulin resistance, in the absence of overt hyperglycemia [21]. These findings indicating that factors, other than increased intracellular glucose concentrations, may predispose to increased sorbitol pathway activity, support and complement previous observations in models of non-diabetic conditions i.e., myocardial ischemia [22,23] and aging [24,25]. Studies of the effects of HFD on sorbitol pathway enzyme gene and protein expression may help to identify an important mechanism contributing to neuropathy and cardiovascular disease in overweight and obese individuals.

Negative consequences of the sorbitol pathway hyperactivity under diabetic conditions include intracellular sorbitol accumulation and resulting osmotic stress, and generation of fructose, a 10-times more potent glycation agent than glucose as well as fructose 1-phosphate [26]. One group reported that increased flux through SDH leads to so called "pseudohypoxia" i.e. an increased free cytosolic NADH/NAD^+ ratio [11] whereas others [27] did not find a relation between cytosolic or mitochondrial NAD^+/NADH redox state and SDH activity in the peripheral nerve. Two groups obtained the results indicating that increased AR, but not SDH, activity contributes to PDN [28, 29].

The role for AR in PDN has been reviewed in detail [30]. New evidence for the key role of AR in functional, metabolic, and morphological manifestations of PDN has been generated in both experimental studies in animal and cell culture models of diabetes and clinical trials of AR inhibitors (ARIs). Our group demonstrated that metabolic abnormalities of early PDN, such as mitochondrial and cytosolic NAD^+/NADH redox imbalances and energy deficiency, can be reversed with an adequate dose of ARI i.e., the dose that completely suppressed diabetes-associated sorbitol pathway hyperactivity [31]. Of particular interest are the results implicating increased AR activity in high glucose- and diabetes-induced oxidative–nitrosative stress [31-35] and downstream events such as activations of mitogen-activated protein kinase (MAPK) [36,37], PARP [35], COX-2 [38], and NF-κB [39]. AR inhibitors have been reported to counteract diabetes-induced loss of two major non-enzymatic antioxidants, GSH and ascorbate, lipid peroxidation, as well as nitrotyrosine formation in peripheral nerve [20,21,35], spinal cord [20], DRG [20] and epineurial arterioles [35] and superoxide production in vasa nervorum [35]. Our group has also demonstrated the key role for AR in diabetes-associated PARP activation in peripheral nerve, spinal cord, DRG, and high glucose-exposed human Schwann cells (HSC) [20,21,35]. AR plays a key role in diabetes-related MAPK activation in DRG neurons [13,37]. Both PARP activation and MAPK activation are involved in transcriptional regulation of gene expression, via the transcription factors NF-κB, activator protein-1, p53, and others [40,41]. Activation of these transcription factors leads to upregulation of inducible nitric oxide synthase, cyclooxygenase-2, endothelin-1, cell adhesion molecules and inflammatory genes [40,42]. Thus, the demonstration of a major contribution of AR to oxidative–nitrosative stress and PARP and MAPK activation in tissue-sites for diabetic complications allows to predict that in the near future the link between increased AR activity and altered transcriptional regulation and gene expression will be established. *Any* product of genes controlled via PARP- and MAPK-dependent transcription factors, regardless of how unrelated to the sorbitol pathway this product looks from a biochemical point of view, will be affected by a diabetes-associated increase in AR activity, and amenable to control by AR inhibition. In accordance with this premise, the most recent findings have shown that increased AR activity leads to activation of NF-κB and activator protein-1 [39], and is responsible for diabetes-induced COX-2 upregulation in the spinal cord oligodendrocytes [38] and 12/15-lipoxygenase overexpression in sciatic nerve [21].

The role for AR in the pathogenesis of PDN is supported by findings obtained in AR-overexpressing and AR-knockout mice. Induction of STZ-diabetes in the mice transgenic for human AR resulted in a more severe peripheral nerve sorbitol and fructose accumulation, MNCV deficit, and nerve fiber atrophy than in their non-transgenic littermates [19]. Treatment of diabetic transgenic mice with the AR inhibitor (ARI) WAY121–509 significantly prevented sorbitol accumulation, MNCV slowing, and the increased myelinated fiber atrophy in diabetic AR-overexpressing mice [19]. Similar findings have been obtained in another transgenic mouse model that overexpressed AR specifically in the Schwann cells of peripheral nerve under the control of the rat myelin protein zero (Po) promoter [43]. The transgenic mice exhibited a significantly greater reduction in MNCV under both diabetic and galactosemic conditions than the non-transgenic mice with normal AR content. In contrast, AR-deficient mice appeared protected from motor nerve conduction slowing, axonal atrophy, and several metabolic manifestations of PDN [44]. These data lend further support to the important role of AR in functional, metabolic and morphological abnormalities characteristic for PDN.

The findings in transgenic and knockout mouse models are in line with new studies with structurally diverse ARIs. Coppey et al. [45] implicated AR in diabetes-induced impairment of vascular reactivity of epineurial vessels, an early manifestation of PDN, which precedes motor nerve conduction slowing. An ARI treatment prevented the development of thermal hyperalgesia, an event associated with early PDN, in STZ-diabetic rats [46]. Furthermore, structurally different ARIs, at least, partially prevented thermal hypoalgesia in rats with more prolonged STZ-diabetes [46], as well HFD-fed [21] and *ob*/*ob* [20] mice. Tactile allodynia was not prevented by an ARI treatment in either STZ-diabetic rats [46] or *ob*/*ob* mice [20], although tactile withdrawal thresholds in response to light touch with flexible von Frey filaments tended to be higher in *ob*/*ob* mice treated with the ARI fidarestat compared with the corresponding untreated group. New evidence supports the role of AR in the pathogenesis of advanced PDN. A 15-month AR inhibition with fidarestat dose-dependently corrected slowed F-wave, MNCV, and SNCV in STZ-diabetic rats [47]. In the same study, diabetes-induced paranodal demyelination and axonal degeneration were reduced to the normal with such low dose of fidarestat as 2 mg/kg. Other manifestations of advanced PDN such as axonal atrophy, distorted axon circularity, and reduction of myelin sheath thickness were also inhibited. In our study in *ob*/*ob* mice that display clearly manifest intraepidermal nerve fiber loss, a sign of small sensory nerve fiber degeneration, fidarestat treatment partially prevented diabetes-associated decrease in intraepidermal nerve fiber density [20]. The results of several recent clinical trials of ARIs are also encouraging and support applicability of the AR concept to the pathogenesis of human PDN. In particular, a clinical trial with the ARI zenarestat indicates that robust inhibition of AR in diabetic human nerve improves nerve physiology and fiber density [48]. Two double-blind placebo-controlled clinical trials of fidarestat in patients with Type 1 and Type 2 diabetes also provided a proof of efficacy of ARIs ([49], and Arezzo et al., unpublished). In these trials, fidarestat improved electrophysiological measures of median and tibial MNCV, F-wave minimum latency, F-wave conduction velocity and median SNCV (forearm and distal), as well as subjective symptoms of PDN such as numbness, spontaneous pain, sensation of rigidity, paresthesia in the sole upon walking, heaviness in the foot and hypesthesia. These findings are consistent with the results of the most recent open-label, prospective study conducted at 12 hospitals in the central area of Honshu, Japan [50]. Treatment of 22 patients with fidarestat significantly increased vibration perception threshold in the upper and lower limbs. The symptoms such as severity of numbness in the lower limbs, heaviness in the foot, coldness and hot flushes in the