Mini Review

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Biochemical Alterations in Diabetic Neuropathy

Subhashree Venugopal*

VIT University, Tamil Nadu, India

*Corresponding author: Subhashree Venugopal, M.Sc., Ph.D, VIT University, Tamil Nadu, India, E-mail: v_subhashree@hotmail.com

Abstract

Type 2 Diabetes mellitus is a disease which manifests with a variety of cardiovascular risk factors, including hypertension, dyslipidemia and overweight or obesity that contributes to development of long term complications termed diabetic related ailments. Diabetic peripheral neuropathy (DPN) is a debilitating condition affecting as many as one half of all patients with diabetes during the course of their disease. Several metabolic and vascular pathways have been identified as contributors to the pathogenesis of diabetic neuropathy. Diabetic neuropathy encompasses a wide range of clinical and subclinical syndromes from pain to complete loss of sensation. Metabolic and therapeutic approaches have focused on aldose reductase, poly (ADP- Ribose) polymerase, protein kinase C, advanced Glycation end products. Novel approaches to identify targets for treatment of diabetic peripheral neuropathy require cross links between molecular and computational biology methods.

Introduction

Diabetes mellitus is one of the most common non-communicable diseases worldwide. It is the fourth or the fifth leading cause of death in most developed countries, and substantial evidence points to an epidemic of diabetic mellitus in many developing and newly industrialized nations [1].The rapid rise in its prevalence has been driven over recent decades by changes in environment including lifestyle of populations [2]. Chronic hyperglycemia is a well-established cause of micro vascular complications [3]. Peripheral neuropathy is a common complication in patients with diabetes mellitus [4]. Diabetic peripheral neuropathy affects at least 50% of patients with type 1 and type 2 diabetes [5]. Biochemical changes found in diabetic neuropathy are more wide spread and more controversial than anatomic changes [6]. Different hypothesis for the pathogenesis of diabetic complications besides increased polyol pathway activity have been proposed including altered protein kinase C activity, increased oxidative stress and an acceleration of nonenzymatic glycation [7]. Haimanot and Abdulkadir [8] also suggested a relation between diabetic neuropathy and duration of diabetes, but no relation between neuropathy and the age of patients. Therefore, 10% of the diabetic population diagnosed for less than one year suffers of neuropathy while this number increases to up to 50% of the diabetic population diagnosed for more than 25 years. It is generally accepted that 30% of the diabetic population suffers from diabetic neuropathy.

Pathogenesis and clinical indications of diabetic peripheral neuropathy

Diabetic peripheral polyneuropathy (DPN) is a multifactorial disorder arising from hyperglycemia and or insulin deficiency. Two main hypotheses have been proposed for the pathogenesis of diabetic neuropathy although it is not clearly established. One is the metabolic derangement theory, hyperglycemic activation of the polyol pathway leading to accumulation of sorbitol and potential changes in theNAD: NADH ratio may cause direct neuronal damage and/or decreased nerve blood flow [9]. The other is that endoneurial micro vascular lesions which plays an important role in diabetic neuropathy. At present, it is thought that both metabolic and vascular factors play roles in the pathogenesis of clinical neuropathy. The pathophysiological mechanisms of diabetic neuropathy (DN) are complex and involve the activation of numerous pathways involving nerve growth factors, inflammatory mediators, and reactive oxygen and nitrogen species [10]. Advanced DPN causes serious complications such as diabetic foot ulcers, gangrene and charcot joint, all of which reduce the quality of life of patients with DPN [11]. DPN is often characterized by damage to both large as well as small thinly myelinated C fibers. Small fiber DPN is associated with increased morbidity and mortality [12]. Symptoms include numbness, pain and decreased sensation as well as autonomic symptoms such as anhidrotic skin, orthostatic hypotension, resting tachycardia, hypoglycemia unawareness, delayed gastric emptying, decreased bladder tone and impotence [12].

Biochemical Factors and Diabetic Neuropathy

Na+/K+ ATPase activity

The factors include decreased Na^+/K^+ ATPase activity, increased anaerobic glycolysis, increased myoinositol, nerve ischemia due to microangiopathy [13]. From biochemical studies in rat diabetic models, it is known that decreased Na^+/K^+ ATPase activity in diabetic subjects reverses rapidly after normalization of blood glucose levels [14]. There is a reduction in catecholaminergic neuronal ability with a reduction in catecholamine synthesis associated with a difficulty to release the neurotransmitters from synaptic terminals [6]. The study reported that alterations in catecholamine metabolism are dependent on the severity and duration of diabetes. Short term diabetes is accompanied with increase or no change in catecholamine content or release, but reduced release and increased storage of catecholamines are found in long term diabetes [15].

Advanced glycation end products

The enhanced formation of advanced glycation end products (AGEs) induced by hyperglycemia has been implicated in pathogenesis of diabetic complications [16]. The oxidative stress may accelerate auto oxidation of glucose to dicarboxyl compounds (glyoxal) that are precursors of N-Ɛ(carboxymethyllysine) (CML) [17] and glycooxidation of amadori products to CML [18]. The main source of reactive oxygen species in diabetes is thought to be mitochondria mediated or mitochondria dependent [19].

Uncoupled proteins

Uncoupled proteins (UCPs) can provide a controlled leak of protons across the inner membrane of mitochondria, thus uncouple oxidative phosphorylation from respiration with a concomitant decrease in mitochondrial membrane potential [20] and free radical generation [21]. UCP2 which is expressed in various human tissues, is thought to control body temperature, energy metabolism as well as to regulation of mitochondrial production of ROS (Reactive Oxygen species). Hence, UCP2 gene is considered to be involved in DPN. A study revealed that the -866 G/A and A/A genotypes of UCP2 are significantly associated with nerve conduction slowing and impaired blood pressure regulation on a head-up tilt test. This suggests that higher UCP2 activity related to the A allele of - 866 G/A polymorphism that causes deterioration of peripheral nerve function by energy depletion rather than neuroprotective effect against oxidative stress in type 2 diabetic patients [22].

Polyol pathway

Elevated blood glucose in diabetic patients leads to increased activity of aldose reductase, anenzyme that converts glucose to sorbitol, one of the alcohol sugars. The result is accumulation of sorbitol within nerves, which is associated with oxidative stress and nerve damage. The polyol pathway secondarily converts sorbitol into fructose .The polyol pathway plays an important role in the development and progression of diabetic neuropathy. Enhanced catabolism of glucose via polyol pathway is known to augment reactive oxygen species by mechanisms such as glutathione depletion or increased prostaglandin synthesis [23]. Superoxide dismutase is known to lose its activity as a consequence of reacting with reducing sugars or other intermediate metabolites which in turn augments radical species [24]. Diabetes is one of the diseases that activates ubiquitin proteasome pathway and it has been proposed that activation of this pathway is responsible for wasting muscle because of insulopenia. The activation of ubiquitin proteasome pathway in some neuronal diseases and insulopenia suggests that ubiquitin may play a role in diabetic neuropathy [25].

Oxidative nitrosative stress manifest by accumulation of lipid peroxidation products, 4 hydroxynonal adducts nitrated proteins and 8-hydroxy guanosine in peripheral nerve, spinal cord and dorsal root ganglion neurons of diabetic rats or mice [26]. Oxidative nitrosative stress is a key mechanism contributing to nerve blood flow and nerve conduction deficits, small sensory nerve fibre dysfunction and morphological manifestation of diabetic peripheral polyneuropathy.

Metanx

Metanx containing 1-methyl folate, pyridoxal 5' phosphate and methylcobalamine was evaluated on oxidative nitrosative stress and manifestations of DPN in Zucker diabetic fatty acid rats. The high efficacy of metanx is probably explained by its interactions of its components counteracting oxidative nitrosative stress through restoration of eNOS (endothelial nitric oxide synthase) coupling in vasa nervorum. (L-methylfolate), neutralization of superoxide and peroxynitrite (methylcobalamine) and chelation of transition metals and abrogation of advanced glycation end products formation. (Pyridoxal 5' phosphate) [27]. Metanx alleviated sensory neuropathy without affecting MNCV (motor nerve conduction velocity) or morphometric characteristics of large myelinated fibers [27]. Fonsceva et al. [28] conducted a multicenter, randomized, double blind placebo trial consisting of 214 patients for 24 weeks to assess whether Metanx would improve objective measures of diabetic peripheral neuropathy. The study provides evidence that Metanx is a safe and effective therapy for alleviation of peripheral neuropathy symptoms, at least in short term.

Glutathione

The administration of reduced glutathione has partially improved experimental diabetic neuropathy [29]. Experimental diabetic neuropathy results in a reduction in nerve blood flow(NBF) by 50% nerve conduction slowing and a large decrease in glutathione and that lipoic acid supplementation resulted in a dose dependent normalization of NBF and glutathione suggest that neuropathy is due in significant part due to oxidative stress and that improving free radical scavenging capacity is responsible for improvement in NBF and neuropathy and a time and dose dependent improvement in digital nerve conduction velocity [30]. One mechanism of reduced NBF is inhibitory effect of superoxide anion on nitric oxide synthase with resultant decreased NO in Experimental neuropathy [31].

Alpha lipoic acid

Alpha lipoic acid which has been shown to be effective in both somatic and autonomic neuropathies in diabetes, normalizes endoneural blood flow [30] reduces oxidative stress [32] and improves vascular dysfunction [33]. In a placebo controlled trial in patients with diabetic neuropathy, a significant relief of neuropathic symptoms was observed in patients who received alpha lipoic acid [34].

A meta-analysis that combined the results of four randomized trials, including 1258 patients, found that treatment with 600 mg/day of intravenous racemic lipoic acid for 3 weeks significantly reduced the symptoms of diabetic neuropathy to a clinically meaningful degree [35].

Acetyl carnitine

Acetyl carnitine is deficient in diabetic condition. In preclinical studies, substitution with acetyl carnitine corrects perturbation of neural Na+/K+ ATPase, myoinositol, NO, prostaglandin and lipid peroxidation all of which play important early pathogenic roles in diabetic peripheral neuropathy [36].

In a 52 week randomized placebo controlled study of 1257 patients with diabetic neuropathy 2 doses of acetyl carnitine, 500 and 1000 mg/day t.i.d (three times a day) were tested and results demonstrated significant improvement in pain and vibration perception association with improvements in sural nerve morphometry in patients treated with 1000 mg acetyl carnitine t.i.d for one year [37].

Resveratrol

Resveratrol was demonstrated to induce effects that may contribute to the protection of β cells in diabetes. In experiments on pancreatic islets, the ability of resveratrol to reduce insulin secretion was demonstrated; this effect was confirmed in animals with hyperinsulinemia, in which resveratrol decreased blood insulin levels [38]. Using a randomized double-blind placebo-controlled clinical trial, a study examined the effects of resveratrol in lowering blood glucose and other related outcomes (e.g., insulin, metabolic markers, cardiovascular risk factors) in patients with type 2 diabetes. In the randomized, double-blind, placebo-controlled clinical trial study, intake of 1 g/d of resveratrol for 45 days was found to significantly reduce systolic blood pressure, fasting blood glucose, hemoglobin A1c, insulin, and insulin resistance, while HDL (high density lipoprotein) was significantly increased, when compared to their baseline levels [39].

Glyoxalase 1

Glyoxalase 1 (Glo1) and glyoxalase 2 (Glo2) present an enzymatic defense system against glycation that suppresses glycation mediated cell damage [40]. Altered Glo1 activity is associated with late diabetic complications [41]. Increased formation of methylglyoxal in diabetes-associated hyperglycaemia leads to a 2–4 fold increase in modifications of proteins by methylglyoxal to form AGEs at the sites of vascular complications [42]. Glo1 activity was significantly reduced in patients with severe painful neuropathy symptoms for both type 1 and type 2 diabetes mellitus patients. The molecular mechanisms that are linked to the altered activity of Glo1 deserve further investigations. The pathogenesis of type 2 diabetes mellitus is considerably heterogeneous and both glycation stress and inflammation-related processes could be cooperatively driving forces in the development of late complications of diabetes mellitus [43].

Poly (ADP- Ribose) polymerase

In Diabetic neuropathy, elevated glucose level increases the ROS production and these free radicals induce DNA strand breaks, thereby activating PARP. After sensing the DNA damage, PARP gets activated and repairs the DNA by transferring ADP-ribose unit to the nuclear proteins and depletes the intra-cellular NAD. Intra-cellular NAD re-synthesis consumes ATP which further leads to impairment of several NAD dependent pathways like glycolysisand mitochondrial respiration. The energy consuming cycle results in rapid depletion of intra-cellular NAD^+ and ATP pools and ultimately the cell dysfunction [44]. PARP over activation has shown increased sensitivity to mechanical noxious stimuli associated with diabetes [45].

Protein Kinase C

Protein kinase C is overactivated by hyperglycemia and by disordered fatty acid metabolism resulting in increased production of vasoconstrictive, angiogenic and chemotactic cytokines including transforming growth factor, vascular endothelial growth factor inhibitors. Protein kinase C overactivation blocking is a critical step in the pathogenesis of diabetic polyneuropathy via its impact on microvascular mechanism [46].

A number of aldose reductase inhibitors have been developed [47]. But none have achieved success for diverse reasons, one being that not all aldose reductase inhibitors penetrate human peripheral nerves. A paradigm shift is imminent in the research arena of diabetic neuropathy using molecular and bioinformatics approaches to reduce the pain and symptoms experienced in late stages of type 2 diabetes. Multiple biochemical pathways have been implicated in the pathogenesis of diabetic peripheral neuropathy. It has been demonstrated that strict glycemic control alone can decrease the incidence of diabetic complications [48]. However, it is impossible to completely prevent the development of diabetic complications solely by glycemic control. The future therapeutic approach which needs to be reckoned with, must focus on developing novel drugs with better efficacy that elicit better response in patients. Moreover, it is imperative to target critical cellular pathways leading to increased oxidative stress production and thereby to enhance the antioxidant defense potential to mitigate diabetic peripheral neuropathy state.

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