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Review

Diabetic peripheral neuropathy: Current perspective and future directions

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ABSTRACT

Diabetic neuropathy is a heterogeneous group of disorders with extremely complex pathophysiology and affects both somatic and autonomic components of the nervous system. Neuropathy is the most common chronic complication of diabetes mellitus. Metabolic disruptions in the peripheral nervous system, including altered protein kinase C activity, and increased polyol pathway activity in neurons and Schwann cells resulting from hyperglycemia plays a key role in the development of diabetic neuropathy. These pathways are related to the metabolic and/or redox state of the cell and are the major source of damage. Activation of these metabolic pathways leads to oxidative stress, which is a mediator of hyperglycemia induced cell injury and a unifying theme for all mechanisms of diabetic neuropathy. The therapeutic intervention of these metabolic pathways is capable of ameliorating diabetic neuropathy but therapeutics which target one particular mechanism may have a limited success. Available therapeutic approaches are based upon the agents that modulate pathogenetic mechanisms (glycemic control) and relieve the symptoms of diabetic neuropathy. This review emphasizes the pathogenesis, presently available therapeutic approaches and future directions for the management of diabetic neuropathy.

Contents

Abbreviations: 3-DG, 3-deoxyglucosone; AGEs, advanced glycation end products; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AR, aldose reductase; CML, N^{ε}-(carboxymethyl) lysine; DAG, diacylglycerol; DPN, diabetic peripheral neuropathy; DPP-IV, dipeptidyl peptidase-IV; FDA, food and drug administration; GIP, glucose-dependent insulinotropic polypeptide; GlcNAc, UDP-*N*-acetylglucosamine; GLP-1, glucagon-like peptide-1; GSH, reduced glutathione; MAPK, mitogen-activated protein kinase; MG, methylglyoxal; MNCV, motor nerve conduction velocity; MOR-NRI, μ-opioid receptor agonist-norepinephrine reuptake inhibitor; NADPH, nicotinamide adenine dinucleotide phosphate; NCV, nerve conduction velocity; NF-κB, nuclear factor-κB; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NNR, neuronal nicotinic acetylcholine receptor; NNT, number needed to treat; NO, nitric oxide; PDE-3A, phophodiesterase-3A; PHN, post-herpetic neuralgia; PKC, protein kinase C; PTB, N-phenacylthiazolium bromide; RCT, randomized clinical trials; ROS, reactive oxygen species; SNCV, sensory nerve conduction velocity; SNRI, serotonin–norepinephrine reuptake inhibitor; SOD, superoxide dismutase; SR-A, scavenger receptor class A; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic and tetracyclic antidepressant; TNF-α, tumor necrosis factor-α.

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1. Introduction

Chronic diabetes mellitus is associated with various complications such as retinopathy, neuropathy, nephropathy, cardiomyopathy, vasculopathy, dermatopathy and encephalopathy [1]. Diabetic neuropathy has been defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in diabetics after exclusion of other causes (e.g. hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic and secondary to other systemic illnesses) [2,3]. Diabetic peripheral neuropathy (DPN) is characterized by pain, paraesthesia, sensory loss and affects approximately 50% of people with considerable morbidity, mortality and diminished quality of life. The Toronto Consensus Panel on diabetic neuropathy recently defined DPN as a 'symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations resulting from chronic hyperglycemia and cardiovascular risk covariates [4].

Painful symptoms such as burning, tingling ('pins and needles' or paraesthesia), shooting (like electric shock) or lancing (stabbing) are present in around one third of patients with DPN and around 20% of all diabetic patients [4,5]. DPN starts in the toes and gradually moves proximally. Once it is well established in the lower limbs, it affects the upper limbs, with sensory loss following the typical 'glove and stocking' pattern of distribution. Significant motor deficits are not common in the early stages of DPN [4]. These symptoms are generally worse at night and disturb sleep [6]. An abnormality of nerve conduction tests, which is frequently subclinical, appears to be the first quantitative indication of the condition [7]. The patient does not typically complain of weakness, but when symptoms are present, they tend to be sensory in nature. Symptomatic muscle weakness tends to develop later in the disease course. Moreover, DPN is also associated with substantial morbidity including depression, susceptibility to foot or ankle fractures, ulceration and lower-limb amputations [8–11].

2. Pathophysiology

The pathogenesis of DPN has remained the subject of research as well as controversy because of multifactorial underlying cause of diabetic neuropathy. It is the result of various biochemical perturbations. Chronic hyperglycemia seems to be the major culprit in the initiation of various metabolic events underlying DPN. Increased free fatty acids develop insulin resistance and deterioration of β-cell function in the context of concomitant hyperglycemia. Several studies suggested that insulin or C peptide deficiencies or both as such contribute to severe DPN [12]. Combination of direct axonal injury due to the metabolic consequences of hyperglycemia, insulin resistance, toxic adiposity, endothelial injury and microvascular dysfunctions leads to nerve ischemia. Diabetes causes functional deficits in nitric oxide (NO) and alterations in endothelial derived relaxing factor (EDRF) resulting in microvascular reactivity and structural microangiopathy, which adds to the worsening of DPN [13]. Hyperglycemia activates several major, well-characterized biochemical pathways that include activation of the polyol pathway [14], increased advanced glycation end products (AGEs) and their receptors [15], activation of protein kinase C (PKC) [16], mitogen-activated protein kinases (MAPK) [17] and inducible nitric oxide synthase [18]. Furthermore, hypoxia and ischemia [19], elevate cytokines such as tumor necrosis factor (TNF)-α [20] and IL-6 [21], nerve growth factor (NGF) deficiency [22] also play significant etiologic role in DPN. One mechanism that has been recognized to play a significant role in the pathogenesis of sensory neuron damage, is the process of reactive dicarbonyls forming AGEs due to hyperglycemia [23]. Hyperglycemia leads to production of AGEs, which damage target cells by three mechanisms. First, AGEs modify the intracellular proteins; hence their function is altered. Second, AGEs modify extracellular matrix components, which interact abnormally with the receptors for matrix proteins (integrins) on cell. Third, plasma proteins modified by AGE precursors bind to AGE receptors on endothelial cells [24], mesangial cells, microglia and macrophages, inducing receptor-mediated production of reactive oxygen species (ROS). This AGE receptor ligation activates transcription factor nuclear factor-κB (NF-κβ), leading to pro-inflammatory gene expression [25]. It includes expression of cytokines and growth factors by macrophages and mesangial cells (IL-1β, IGF-1, TNF-α, TGF-β, macrophage-colony-stimulating factor, granulocyte-macrophage-colony-stimulating factor and platelet-derived growth factor) and expression of pro-coagulatory and pro-inflammatory molecules by endothelial cells (thrombomodulin, tissue factor and VCAM-1). The activation of NF-κβ pathway by hyperglycemia also induces apoptosis in neuronal cells [26,27].

There is convincing experimental and clinical evidence that the generation of ROS increases in both types of diabetes and the onset of diabetes is closely associated with oxidative stress [28]. The disease arises from a combination of microvascular and neuronal deficits. Oxidative stress can contribute significantly to these deficits as a direct result of prolonged hyperglycemia [29]. The transient receptor ankyrin 1 ion channel on primary afferent nerve fibers is involved in the pathogenesis of DPN due to sustained activation by reactive compounds, generated in diabetes mellitus [30]. The AGE, polyol, PKC and hexosamine pathways directly alter the redox capacity of the cell either through direct formation of ROS or by depletion of necessary components of glutathione