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Review

Diabetic neuropathy: therapies on the horizon

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Abstract

Objectives This is a review of emerging interventions from the recent preclinical and clinical literature that demonstrate the potential for effectiveness in the therapy of diabetic neuropathy (DN). DN is the most common complication of diabetes mellitus and up to 50% of patients with type 1 and type 2 forms have some or other form of neuropathy. The pathology of DN is characterized by progressive nerve fibre loss that gives rise to positive and negative clinical signs and symptoms such as pain, paraesthesiae and loss of sensation.

Key findings There are very few drugs available to directly treat DN. Those that are clinically indicated provide symptomatic relief but do not repair or reverse underlying nerve damage. However, some agents are in clinical development that may support adult neurons and direct reparative processes after injury stages. Several disease modifying drugs such as aldose reductase inhibitors and protein kinase C inhibitors are in phase III development. Agents on the horizon include neurotrophic factors, growth factors, gene therapy, immunotherapy, poly(ADP-ribose) polymerase inhibitors and non-immunosuppressive immunophilin ligands.

Summary Progress has been made toward understanding the biochemical mechanisms leading to diabetic neuropathy, and as a result, new treatment modalities are being explored. The pathogenesis, types and approaches for treating DN together with the newer therapeutic interventions on the horizon are discussed.

Keywords diabetic neuropathy; poly(ADP-ribose) polymerase inhibitors; non-immunosuppressive immunophilin ligand

Introduction

Diabetic neuropathies (DNs) are a heterogeneous group of disorders that encompass a spectrum of clinical and subclinical syndromes with differing anatomical distributions, clinical courses and, possibly, present a wide range of abnormalities. DN is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.[1]

In recent years, considerable progress has been made toward understanding the biochemical mechanisms leading to DN and as a result new treatment modalities are being explored. This review discusses emerging interventions and treatment modalities from the recent preclinical and clinical literature that demonstrate the potential effectiveness of therapy of the diverse forms of DN and focuses on the therapies currently on the horizon. DNs are the most common long-term complications of diabetes and are a significant source of morbidity and mortality.[2] DNs account for more hospitalizations than all other diabetic complications combined and are responsible for 50–75% of non-traumatic amputations.[3] In the UK, prevalence estimates have ranged from 5% to as high as 100%[4] and about 7 million individuals are likely to be affected by DN. In India, the number of patients with DN is rapidly increasing, but no systematic prevalence or incidence studies have been conducted and hard evidence is therefore lacking.[5] The annual costs of DN and its associated morbidities in the US have been estimated to exceed $10.9 billion.[6] The symptoms of DN depend upon the type of neuropathy and the nerves affected. Some patients remain asymptomatic, while others may manifest symptoms such as numbness, tingling or pain in the extremities, problems with urination, impotence and weakness.

The optimal strategy and gold standard method for the prevention and treatment of DN remains glycaemic control.

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Currently, very few drugs are available to directly treat diabetic complications. Those that are clinically indicated provide symptomatic relief and do not address the underlying biochemical problems. However, several promising disease modifying drugs are in phase III development. For example, aldose reductase inhibitors (fidarestat, ranirestat and epalrestat), protein kinase C β inhibitors (ruboxistaurin), poly-ADP polymerase inhibitors, antioxidants (α-lipoic acid, vitamin E), phVEGF$_{165}$ gene transfer and prostaglandin analogues have been found effective in phase II trials and phase III trials for these are ongoing.

Current evidence suggests that DN should not be dismissed as an untreatable disorder, and physicians should focus on the accurate diagnosis of this complication in order to offer appropriate therapy to patients.

Types of diabetic neuropathy

Classification of DN was originally proposed by Thomas in 1997.[7] DN can be broadly categorized into two, diffuse and focal neuropathies. Diffuse neuropathies include distal symmetrical sensorimotor polyneuropathy (DPN) and diabetic autonomic neuropathy. They are common, usually chronic and often progressive. The focal neuropathies are less common, usually acute in onset and often self-limited.

The focal forms of DN reflect damage to single (mononeuropathy) or multiple peripheral nerves (mononeuropathy multiplex), cranial nerves, regions of the brachial or lumbosacral plexuses (plexopathy), or the nerve roots (radiculopathy). Figure 1 shows a classification scheme for DN proposed by the American Diabetes Association.[8]

Pathogenesis of diabetic neuropathy

The pathology of DN is characterized by progressive nerve fibre loss that gives rise to positive and negative clinical signs and symptoms such as pain, paraesthesiae and loss of sensation. A number of biochemical mechanisms, including non-enzymatic glycosylation, increases in oxidative stress, neuroinflammation and activation of the polyol and protein kinase C (PKC) pathways, contribute to the development of diabetic neuropathy.

Polyol pathway

Hyperglycaemia raises the intracellular glucose level in nerves, leading to saturation of the normal glycolytic pathway. Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to reduced nerve myo-inositol, decreased membrane Na^+/K^+-ATPase activity, impaired axonal transport and structural breakdown of nerves, causing abnormal action potential propagation.[9]

Advanced glycation end products

The non-enzymatic reaction of excess glucose with proteins, nucleotides and lipids results in advance glycation end products.[10,11] Collectively, the biochemical damage induced by advanced glycation end products results in impaired nerve blood flow and diminished neurotrophic support,[12] and may have a role in disrupting neuronal integrity and repair mechanisms.

Oxidative stress

The increased production of free radicals in diabetes may be detrimental through several mechanisms that are not fully understood. These include direct damage to blood vessels leading to nerve ischaemia and facilitation of advanced glycation end-product reactions. Despite the incomplete understanding of these processes, use of the antioxidant α-lipoic acid may hold promise for improving neuropathic symptoms.[13]

Protein kinase C

Hyperglycaemia activates PKC production, which initiates a complex intracellular signalling cascade, affecting gene expression in many organs and tissues throughout the body.[14] PKC activation increases retinal and renal blood flow, as well as vascular contractility and permeability. PKC activation has been linked most closely with retinopathy and neuropathy.

Figure 2 is a schematic representation of the liaison between hyperglycaemia and the development of DN. High intracellular levels of glucose can undergo autoxidation, lead to the formation of advanced glycation end products and activate

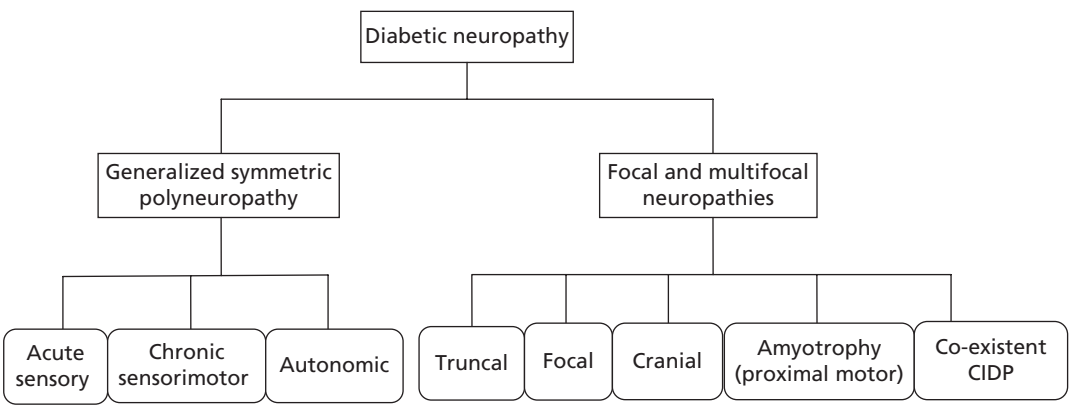

Figure 1 Classification scheme proposed by the American Diabetes Association for diabetic neuropathies.[8] CIDP, chronic inflammatory demyelinating polyneuropathy.

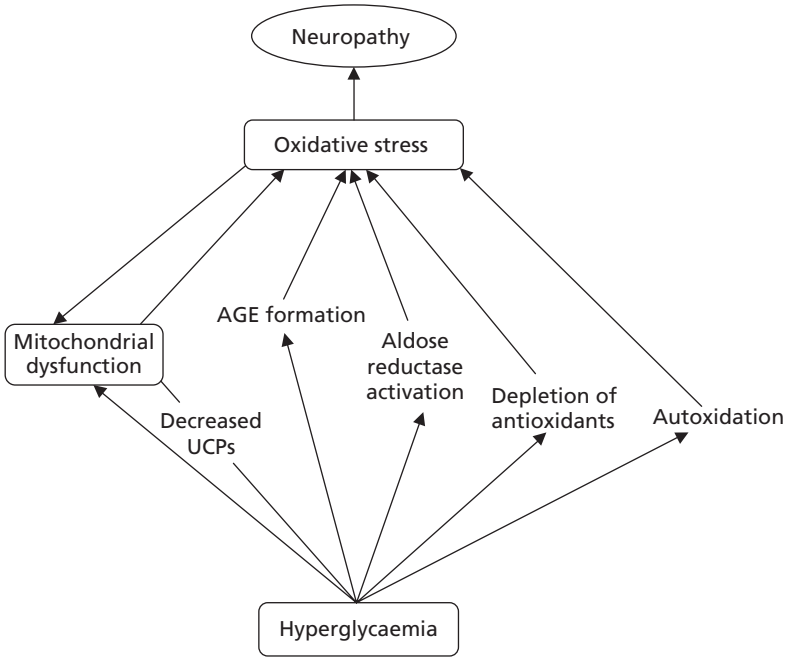

Figure 2 Schematic representation of the liaison between hyperglycaemia and the development of diabetic neuropathy. AGE, advanced glycation end products; UCPs, uncoupling proteins.

aldose reductase which, together with osmotic stress, can cause depletion of antioxidants. The presence of oxidative stress can lead to mitochondrial dysfunction, resulting in a vicious cycle where the mitochondria produce more reactive oxygen species (ROS) in response. High glucose may also cause increased flux of NADH through the electron transport chain and may decrease expression of uncoupling proteins, both of which favour increased mitochondrial ROS production, leading to oxidative stress.

Approaches to treating diabetic neuropathy

The treatment for DN has two aims, symptomatic treatment and nerve regeneration. Most of the clinically available therapies are primarily symptomatic and are directed at pain control and foot care; specific therapy for nerve regeneration or damage is disappointing. Newer therapies are being developed to treat underlying nerve regeneration or damage.

Treatment options for neuropathic pain

Treatments for neuropathic pain include tricyclic antidepressants, anticonvulsants, selective serotonin reuptake inhibitors, dual reuptake inhibitor antidepressant (duloxetine), local anaesthetic antiarrythmics (lidocaine, mexiletine), opioids, topical agents (capsaicin, lidocaine), sympatholytic agents (clonidine), NMDA antagonists (dextromethorphan, ketamine, amantadine, memantine) and miscellaneous agents (levodopa, α-lipoic acid, baclofen, nerve growth factor and γ-linolenic acid, methylcobalamin, bupropion)[15,5] which are clinically available for neuropathic pain relief and amelioration.

Treatment and therapies on the horizon

Various newer therapies are currently on the horizon and their role is being explored to determine their potential in treating DN. They include gene therapy, immunotherapy, aldose reductase inhibitors, poly(ADP-ribose) polymerase (PARP) inhibitors, non-immunosuppressive immunophilin ligand, new peptide-based therapies such as C-peptide, islet neogenesis-associated protein (INGAP) peptide, antioxidant therapy (lycopene, α-lipoic acid, acetyl-L-carnitine, erythropoietin derivatives, substance P receptor inhibitors, cyclooxygenase inhibitors, advance glycation end-product inhibitors and glutamate carboxy peptidase II inhibitors (see Table 1).

Gene therapy

Rat models for gene transfer of vascular endothelial growth factor via a herpes simplex virus vector prevent loss of skin nerve fibres and reduce neurotransmitter markers (neuropeptides calcitonin gene-related peptide and substance P) associated with neuropathy.[16] The delivery of the neovascularization-inducing embryonic morphogen sonic hedgehog has been shown to induce vasculature in sciatic nerves in diabetic rats.[17] Intramuscular injections of liposomal haemagglutinating virus of Japan/human hepatocyte growth factor gene in a diabetic rat model increased the density of endoneurial capillaries and improved nerve conduction velocity and amplitude.[18]

Growth factors

There is now considerable evidence from animal models of diabetes that decreased expression of nerve growth factor and its receptor, trk A, reduces retrograde axonal transport of nerve growth factor and diminishes support of small unmyelinated neurons and their neuropeptides, such as substance P and calcitonin gene-related peptide, both potent vasodilators.[19,20]

Table 1 Treatment of diabetic neuropathy based on putative pathogenetic mechanism

Compound	Abnormality	Aim of treatment	Status of randomized clinical trials	Reference
Aldose reductase inhibitors	Polyol pathway↑	Nerve sorbitol↓		
Fidarestat			Effective in phase II trials	28
Ranirestat			Effective in phase II trials	30
Epalrestat			Marketed in Japan	31
Myo-inositol	Nerve myo-inositol↑	Myo-inositol↓	Equivocal	51
α-Lipoic acid	Oxidative stress↑	Oxygen free radical↓	Effective in randomized clinical trials (studies ongoing)	50
Lycopene	Oxidative stress↑	Oxygen free radical↓	Studies ongoing	49
phVascular endothelial growth factor gene transfer	Nerve hypoxia↑	Angiogenesis↑	Phase III trial ongoing	18
Protein kinase C β inhibitor (ruboxistaurin)	Protein kinase C↑	Nerve blood flow↑	Phase III trial ongoing	45
C-peptide	C-peptide↓	Nerve blood flow↑	Effective in phase II trial	35
Poly(ADP-ribose) polymerase inhibitor (GPI-15427)	DNA damage	DNA repair	Studies ongoing	33

Drugs that have shown some promise are included.

Furthermore, recombinant human nerve growth factor administration restores these neuropeptide levels toward normal and prevents the manifestations of sensory neuropathy in animals.[21]

Unfortunately, recombinant human nerve growth factor was not found to have beneficial effects over and above the placebo. The reason for this contradiction is yet to be resolved, a setback for growth factor therapy of DN.

Lately, there have been rapid strides in the understanding of a diverse array of neurotrophic factors, growth factors and other biological agents. These agents are capable of supporting adult neurons and direct reparative processes after injury to the nervous system. Understanding the mechanisms by which these factors operate offers the opportunity to utilise these factors. These factors manipulate relevant signal transduction pathways and thus can be used as therapeutics for a wide range of neurodegenerative diseases, including diabetic neuropathy.[22]

Recent advances in directly assessing the progression of nerve damage in diabetic patients will hopefully facilitate renewed clinical evaluation of treatments for degenerative DN and may provide the framework for advancing the potential of growth factors as therapy for currently untreatable conditions.

Immunotherapy

Immunotherapy is an emerging treatment used particularly in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) along with distal symmetric polyneuropathy. Both multifocal axonal neuropathies caused by inflammatory vasculopathy and CIDP were responsive to immunotherapy comprising immunoglobulin and steroids. The former condition is seen mostly in non-insulin-dependent diabetes mellitus and demyelinating neuropathy, and is indistinguishable from the latter condition, which occurs mainly with insulin-dependent diabetes mellitus.

Intravenous immunoglobulin treatment was found to be successful in the treatment of diabetic amyotrophy. Immunosuppressive therapy comprising corticosteroids, intravenous immunoglobulin and cyclosporine has improved aggressive mononeuritis multiplex in the patient with diabetes.[23–25] In a recent clinical study, the neuropathy impairment score significantly improved in 80% of patients with diabetes and polyneuropathy who met the electrophysiologic criteria for CIDP.[25] Cocito *et al*. reported intravenous immunoglobulin as a first-line treatment and successfully treated patients with CIDP.[24]

Clinical studies show immunotherapy to be beneficial in patients with a particular form of DN. However, further clinical studies are warranted to prove its effectiveness.[24,26]

Aldose reductase inhibitors

The involvement of the sorbitol pathway in diabetic complications has given mechanistic insights into the biochemistry of complications and since then the key enzyme aldose reductase has been an attractive pharmacologic target. Aldose reductase converts cytosolic glucose to sorbitol by NADPH oxidation; another enzyme, sorbitol dehydrogenase, converts sorbitol to fructose by NAD^+ hydrogenation.[27]

Aldose reductase inhibitors have been effective in preventing the development of DN in numerous animal models, however clinical trials of these compounds have not yielded much. A variety of aldose reductase inhibitors have been studied and almost all of them have reduced nerve polyol levels and thus the pain and DN symptoms.

Ranirestat (AS-3201) is a well-tolerated spirosuccinimide aldose reductase inhibitor discovered in 1998. It is a potent aldose reductase inhibitor that reduces sorbitol levels and improves motor nerve conduction velocity (NCV) in streptozotocin (STZ)-induced diabetic rats. Kinetic analyses show its inhibition of aldose reductase to be reversible and uncompetitive.[28] Phase II trials showed promising results with few side-effects and marked improvement in both NCV deficit and DN symptoms.[29] However, definitive phase III study conclusions could not be drawn as of July 2007 due to the unusually high placebo effect. AS-3201 development is continuing and researchers hope that continued study and increased dosage of ranirestat will prove effective in future DN treatment.[30]

Epalrestat entered the Japanese market in 1992 as a carboxylic acid aldose reductase inhibitor with minimum side-effects but without conclusive evidence of efficacy backed by a randomized, double blind placebo-controlled study. A study conducted during the period 1997 to 2003 reported that it delayed nerve deterioration and alleviated many common DN symptoms such as limb numbness and cramping at slightly elevated doses (150 mg).[31] Although these results have not been replicated, it is now standard drug therapy for DN in Japan.

Poly(ADP-ribose) polymerase inhibitors

PARP inhibition has recently been identified as a novel approach to the treatment of experimental peripheral diabetic neuropathy. PARP is a nuclear enzyme associated with DNA repair and is overactivated by oxidative DNA damage, depleting NAD^+ and thereby slowing the rate of glycolysis, electron transport and ATP formation. PARP inhibition alleviates numerous experimental pathologic conditions associated with oxidative stress.[32] Preclinical studies have shown that aldose reductase inhibitors sorbinil or fidarestat inhibit poly(ADP-ribose) accumulation in diabetic nerve and retina. Studies on STZ-induced diabetic rats treated with PARP inhibitor and STZ-diabetic PARP-deficient mice have shown the role of PARP activation in peripheral neuropathy, which provides the rationale for the development of orally active potent PARP inhibitors (GPI-15427) and PARP inhibitors containing combination therapies for the prevention and treatment of this devastating complication of diabetic mellitus.[33]

Non-immunosuppressive immunophilin ligand

Immunophilins are receptors for the immunosuppressant drugs. FK1706 is a novel non-immunosuppressive immunophilin ligand with neurotrophic activity and favourable pharmacokinetic profile, and may represent a critical opportunity to meet the significant unmet medical needs of painful DN.[34]

C-peptide

C-peptide is a 31 amino-acid peptide connecting the A and B chains of proinsulin. This insulin precursor molecule, having a plasma half-life of 20–30 min,[35] helps in the proper folding of insulin. Originally perceived as biologically inactive, it has now been established that in human skeletal muscle it causes glucose uptake and has certain insulinomimetic action. In various neural cells it has caused amino acid uptake and exerted insulin-like effects.[36]

It stimulates Na^+ and K^+ ATPase activity in peripheral nerves in diabetic animals, indicating that it has the potential to ameliorate the abnormalities in ion fluxes across cell membranes that are characteristics of DPN.[37,38] It promotes vasodilation in endothelial cells through stimulation of nitric oxide synthase, suggesting that it may provide neurotrophic support in DPN. Preclinical studies on BB/W type 1 diabetic rats reported improved peripheral NCV and reduced axonal nerve degeneration.[38]

Limited clinical trials have confirmed its beneficial effects on autonomic and somatic nerve function in patients with type 1 DPN. However, further investigations are warranted to evaluate the benefits of C-peptide for use in treating DPN, especially because it is not clear whether NCV changes actually contribute to the symptoms experienced by diabetic patients.

Islet neogenesis-associated protein peptide

INGAP peptide is a synthetic pentadecapeptide comprising a biologically active portion (amino acids 104–118) of INGAP. Preclinical studies have shown that INGAP and INGAP peptide are capable of inducing the formation of new islets of Langerhans in the pancreas. A STZ-induced type 1 diabetic mice model showed reversal of hyperglycaemia on chronic administration of INGAP peptide,[39] and a more recent study reported in-vitro insulin secretion by INGAP peptide. INGAP peptide administration in STZ-induced diabetic mouse models has shown correction in sensory dysfunction and upregulation of the expression of proteins involved in nerve regeneration such as tubulin and actin in an insulin-independent manner.[40] Phase II clinical trials of INGAP peptide for type 1 and type 2 diabetes have been completed but the results are still to come.

Protein kinase C-β inhibitor

Elevated levels of PKC have been linked to renal, retinal and cardiovascular complications but its association with DN remains unclear. Recently, experimental studies suggest that PKC activation also contributes to neural complications in STZ-induced diabetic animals.[41–43] Hyperglycaemia-induced oxidative stress may also mediate the adverse effects of PKC-β isoforms by activating the diacylglycerol-PKC pathway.[41] The activation of PKC contributes to the generation of superoxide anion radicals through phosphorylation of NADH oxidase.[44] Preclinical studies have shown PKC inhibition by a PKC-β selective inhibitor, LY333531, prevented deficits in NCV and sciatic nerve blood flow.[42] In the same study, myo-inositol depletion was also corrected by LY333531 and NZ-314, an aldose reductase inhibitor. The beneficial effects in preventing the development of diabetic nerve dysfunction are through inhibition of PKC-β by linolenic acid, which was stated to be mediated through the action of LY333531 on the endoneural microvasculature.

A phase II clinical study found a PKC-β inhibitor (ruboxistaurin) to be well tolerated and to improve neuropathic symptom scores.[45] US Food and Drug Administration approval was sought by Eli Lilly to market ruboxistaurin as a pharmaceutical agent for diabetic retinopathy but for unknown reasons the company withdrew its marketing application in March 2007 and its fate is currently unclear.

Acetyl-L-carnitine

Acetyl-L-carnitine has sparked clinical interest for its analgesic effect in different forms of neuropathies and has established prophylactic and therapeutic potential for treating DN especially in hypoalgesia.

In experimental studies, substitution with acetyl-L-carnitine has corrected disorders of neural Na^+/K^+ ATPase, myo-inositol, nitric oxide, prostaglandins and lipid peroxidation, all of which play important early pathogenetic roles in DPN.[46,47] Clinical studies have also shown that acetyl-L-carnitine is efficacious in the treatment of painful neuropathies.

Convincing data have been obtained from a preclinical study that has highlighted the importance of acetyl-L-carnitine in progressive DN.[48] In a clinical trial, with a dose of 1000 mg three times a day for 1 year, acetyl-L-carnitine considerably reduced symptoms, particularly pain, and improved nerve fibre regeneration and vibration perception in patients with established DN.[46,47]

Antioxidant therapy

Antioxidants have proven efficacy against neural and vascular complications caused by ROS damage. Newer antioxidant agents such as lycopene and α-lipoic acid have made antioxidants an indispensible part of the newer therapeutic regimen for DN treatment.

Lycopene is a carotenoid found mainly in tomatoes and tomato products. The development of tolerance, inadequate relief and potential toxicity of classical antinoceptive agents led to the discovery of this novel antinociceptive agent. It has powerful antioxidant properties with singlet-oxygen-quenching capacity 47- and 100-times greater than that of β-carotene and vitamin E, respectively.

In preclinical studies on diabetic mice, lycopene significantly attenuated thermal hyperalgesia and inhibited tumour necrosis factor α and nitric oxide release in a dose-dependent manner. Experimental studies conclude that it can be a therapeutic option in the treatment of neuropathic pain associated with diabetic mellitus. It has reversed the hyperalgesic stage of DN similar to stage I in human DN. Its effect on stage II, that is the hypoalgesic phase, needs to be further tested in a different animal model. Its mechanism of action remains elusive but it probably acts through inhibition of nitric oxide and tumour necrosis factor α release.[49]

α-Lipoic acid or thioctic acid has been approved for the treatment of DN in Germany since the 1960s. It is a free radical scavenger and transition metal chelator with potent antioxidant properties, and prevents neuronal and neurovascular injury in animal models of DN.[50,51] Resveratrol is the most widely assessed botanical compound extracted from red grapes. Studies in STZ-treated rats demonstrated attenuation of thermal hyperalgesia and cold allodynia as well as decreases in oxidative stress, DNA damage and nerve conduction deficits;[52,53] similarly, in type I diabetic mice, resveratrol prevents neuropathic pain.[54] Experimental studies with STZ-induced rats found that α-lipoic acid has mostly beneficial effects on DN. Clinical trials reported that α-lipoic acid use relieved painful neuropathic symptoms and autonomic neuropathy symptoms, and thus significantly improved quality of life.[55–57] Intravenous administration of α-lipoic acid (600 and 1200 mg) significantly reduced the total symptom score (pain, burning, paraesthesiae and numbness) in patients with neuropathic symptoms.[55] Conjugation therapy using α-lipoic acid has synergistic therapeutic effects on peripheral nerve functions.[58–60] It is likely to provide additional therapeutic benefits in type 2 diabetes mellitus patients because it activates the *SIRT1* genes that regulate glucose metabolism and insulin sensitivity.[61–63]

Pharmacologically, lipoic acid improves glycaemic control and polyneuropathies associated with diabetes mellitus, and effectively mitigates toxicities associated with heavy metal poisoning. As an antioxidant it directly terminates free radicals, chelates transition metal ions, increases cytosolic glutathione and vitamin C levels and toxicities associated with their loss. These diverse actions suggest that it acts by multiple mechanisms, both physiological and pharmacological. Currently, particular attention is being paid to the potential benefits of lipoic acid with respect to glycaemic control, improved insulin sensitivity, oxidative stress and neuropathy in diabetic patients.[64] It is undergoing extensive trials in the US as an antidiabetic agent and as a therapy for distal symmetric polyneuropathy.

Erythropoietin derivatives

Recent work has discovered the neuroprotective properties of erythropoietin, a 34-kD protein associated with haematopoiesis. Erythropoietin receptor is expressed in central neurons, astrocytes and glia as well as in sensory neurons.[65] In central neurons, erythropoietin has shown protection against focal ischaemia. However, it has met with setbacks such as excessive red cell production and development of auto-antibodies.[66] The development of small peptides based on the biologically active portion of erythropoietin and strategies to protect such peptides against cellular degradation is continuing.

Substance P receptor inhibitor

A recent randomized study found no improvement in neuropathic symptoms and objective parameters with substance P receptor inhibitor (NK-1 receptor antagonist).[67]

Cyclooxygenase inhibitors

The polyunsaturated fatty acids have been a major target for ROS damage, and elevated oxidative stress impairs the nerve membrane structure. An experimental diabetes mellitus model showed that rats with STZ-induced diabetes had higher levels of the cyclooxygenase-2 (COX-2) protein than non-diabetic rats and the inhibition of selective COX-2 prevented reduction of mean NCV and nerve blood flow. Selective COX-2 pathway inhibition by meloxicam has prevented reductions in NCV and nerve blood flow.[68,69] Therefore, the activation of the COX-2 pathway may be an additional factor implicated in the development of DN.

Advanced glycation end-product inhibitor

Experimental studies on STZ-induced diabetic neuropathic rat models have shown improvement in NCV by aminoguanidine, an inhibitor of advanced glycation end-product formation and a free radical scavenger.[70,71]

Recently, it has been reported that OPB-9195 treatment improved tibial motor NCV and restored the decrease in sciatic nerve Na^+/K^+ ATPase activity in diabetic rats, which was in parallel with suppression of oxidative stress-induced DNA damage.[72,73]

Controlled clinical trials to determine its efficacy in humans have been discontinued because of toxicity, including flu-like syndrome, gastric disturbances and anaemia.[73,74] Despite promising results with aminoguanidine, it is unlikely to be used for therapeutic purposes.

Glutamate carboxypeptidase II inhibitors

Glutamate carboxypeptidase II is a neuropeptidase that hydrolyses the neuropeptide *N*-acetyl-aspartylglutamate to liberate free glutamate, which is believed to be responsible for neuropathic pain and to contribute to progressive nerve dysfunction and degeneration in diabetes. Therefore, glutamate carboxypeptidase II inhibition was suggested to produce a neuroprotective effect by attenuating the free glutamate release induced by ischaemia.[26,75]

Summary

New strategies are necessary that directly address the underlying nerve damage or nerve degeneration in DN. Reports from preclinical and clinical studies with inhibitors implicated in the pathogenesis of DN have shown encouraging results but only time will tell whether and how these will translate into therapeutics. To date, only a few of them have been made clinically available. Gene therapy and immunotherapy are a big step forward in treating the underlying nerve damage. Discovery of newer antioxidants such as lycopene and α-lipoic acid has given a new dimension to the treatment of neuropathic pain. Unravelling the role of PARP in the pathology of oxidative stress-induced nerve damage has led to the development of a potent oral PARP inhibitor. Dual-action peptides such as C-peptide, INGAP peptide and erythropoietin derivatives are other promising candidate molecules with multiple corrective effects that might prove to be the first effective treatment of DN, especially diabetic peripheral neuropathy. The development of drugs to treat DN is the real challenge and further exhaustive and intensive work needs to be done in this regard.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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