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Inflammation: Therapeutic Targets for Diabetic Neuropathy

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Abstract There are still no approved treatments for the prevention or of cure of diabetic neuropathy, and only symptomatic pain therapies of variable efficacy are available. Inflammation is a cardinal pathogenic mechanism of diabetic neuropathy. The relationships between inflammation and the development of diabetic neuropathy involve complex molecular networks and processes. Herein, we review the key inflammatory molecules (inflammatory cytokines, adhesion molecules, chemokines) and pathways (nuclear factor kappa B, JUN N-terminal kinase) implicated in the development and progression of diabetic neuropathy. Advances in the understanding of the roles of these key inflammatory molecules and pathways in diabetic neuropathy will facilitate the discovery of the potential of anti-inflammatory approaches for the inhibition of the development of neuropathy. Specifically, many anti-inflammatory drugs significantly inhibit the development of different aspects of diabetic neuropathy in animal models and clinical trials.

Keywords Inflammatory cytokine · Adhesion molecule · Chemokine · Diabetic neuropathy · Pathways · Anti-inflammation

Introduction

On September 14, 2011, the International Diabetes Federation announced that 336 million people worldwide had type 2 diabetes and that this disease was responsible for 4.6 million deaths each year. Diabetic neuropathy is the most common complication of type 2 diabetes and affects approximately 50 % of patients over the course of their disease [1]. Diabetic neuropathy has typical characteristics such as pain, numbness, tingling, weakness, and difficulties with balance. Ultrathin sections of the sciatic nerve reveal that the thickness of myelin sheaths is reduced in small, medium-sized, and large axons, and the basement membrane of endoneural microvessels is thickened in db/db mice, a model of peripheral diabetic neuropathy [2]. Diabetic neuropathy can develop even after the initiation of strict blood glucose control due to a phenomenon termed "metabolic memory" [3]. In the absence of more specific drugs, early diagnosis and intensive glycemic control can, however, significantly reduce the incidence of neuropathy in diabetic subjects.

Hyperglycemia, dyslipidemia, and insulin resistance are involved in diabetic neuropathy [4]. Before the development of overt hyperglycemia and diabetes in patients with the metabolic syndrome, the presence of the accumulation of sorbitol, oxidative stress, and 12/15-lipoxygenase activation indicate that additional factors must link diabetes and peripheral neuropathy (Fig. 1) [5]. Biochemical factors resulting from the diabetic state contribute to oxidative stress and nerve damage in diabetic neuropathy. Glucose and lipoproteins interact with various receptors on neurons and microvascular endothelial cells. Diabetes-modified (oxidized and glycated) proteins and lipoproteins bind additional receptors. These receptors include transporters that internalize glucose and lipids, which can accumulate intracellularly and disrupt mitochondrial metabolic pathways. The receptors also initiate inflammatory signaling mechanisms that directly result in oxidative stress and increase the expression and activity of oxidative and nitrosative enzymes. Oxidative stress has been considered to be the final common pathway of cellular injury in hyperglycemia [6], but the mechanisms leading to diabetic neuropathy are more complex and include damage to mitochondria and other cellular components [7].

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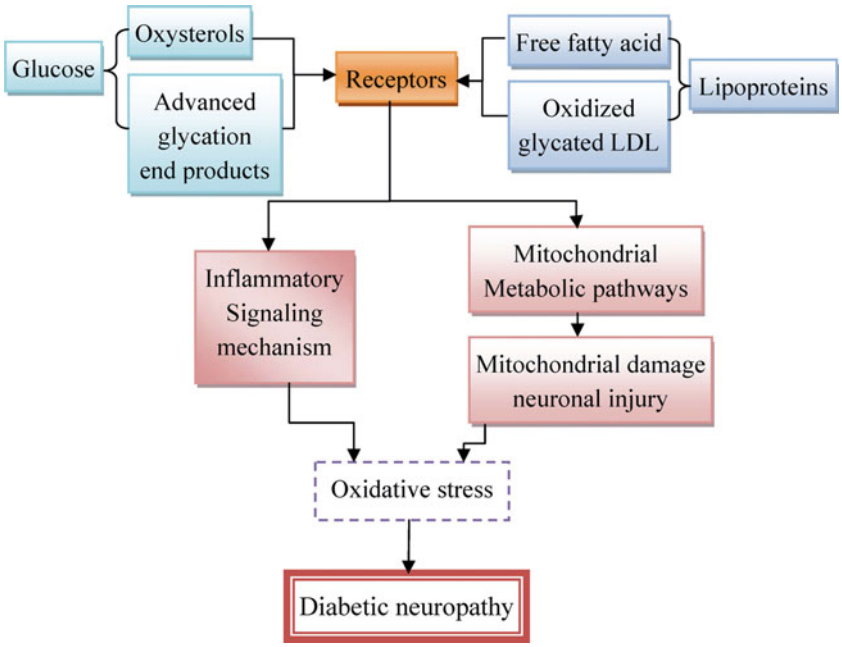

Fig. 1 Summary illustration of the mechanisms that cause diabetic neuropathy. *LDL* low-density lipoprotein

Non-diabetic neuropathy is a general term for disorders of the peripheral nervous system that are not caused by diabetes. According to the Neuropathy Association, 30 % of neuropathies evolve from diabetes, 30 % from unknown causes, and 40 % from infections, autoimmune disorders, genetic factors, nutrient imbalances, tumors, or toxins. The first line of medications used to treat mild symptoms includes over-the-counter pain medications. In more severe cases, doctors may prescribe opiates, other narcotic medications, anti-seizure medications, lidocaine patches, or anti-depressants to relieve symptoms. However, modern medicine cannot reverse neuropathy once it has developed; thus, it is essential to treat the disease as early as possible symptoms of neuropathy are experienced. Anti-tumor necrosis factor-α (TNF-α) therapy or interferon-α therapy may have potential as treatment options for a spectrum of immune-mediated neuropathies, and useful guidelines exist for dose modifications that take advantage of the effects of chemotherapy and reduce neurotoxicity [8]. Chemotherapy-induced peripheral neuropathy and isolated suprascapular neuropathy can initially be treated with broad-spectrum analgesic medications such as non-steroidal anti-inflammatory drugs [9–11], and non-steroidal anti-inflammatory drugs are also used to treat gouty arthritis of the hand and wrist [12].

Recent reviews have focused on the influences of metabolic factors, the interactions of various mechanisms, progress in clinical trials, and how current knowledge should be applied in future therapeutic interventions [4]. This review expands on a previous paper that reviewed many of the inflammatory mediators involved in diabetic neuropathic conditions and provided an overview of the therapeutics that target inflammation [13]. Here, we review the related features of inflammation, the role of inflammation in the pathogenesis of diabetic neuropathy, and new strategies for the treatment of diabetic neuropathy based on agents that target inflammatory pathways.

Molecules and Pathways of Inflammation in Diabetic Neuropathy

Diabetic neuropathy exhibits features of low-grade chronic, subclinical inflammation [4]. Proinflammatory cytokines, such as TNF-α, interleukin (IL)-1, IL-6, IL-8, monocyte chemoattractant protein-1, and C-reactive protein, are mainly produced by activated immune cells but are also produced by resident macrophages and adipocytes and play a role in amplifying inflammatory reactions. Circulating and locally produced intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, and E-selectin, which reflect low-grade chronic inflammation, have been associated with diabetic complications [14]. Chemokines released from infected/injured tissue activate the endothelium to increase the expression of adhesion molecules and chemokines. Here, we discuss some of the potential mechanisms involved in the inflammatory response in this disease (Fig. 2).

Hypoxia

Reductions in blood flow lead to nerve hypoxia and result in diabetic neuropathy. Hypoxia induces the expression of numerous pro-angiogenic and proinflammatory genes in macrophages [15]. Alterations in microvessels are observed in peripheral nerves [16]. In human neuropathy, occlusion of the capillaries that supply the nerves causes ischemic nerve fiber damage and perineural capillary luminal occlusion that is due

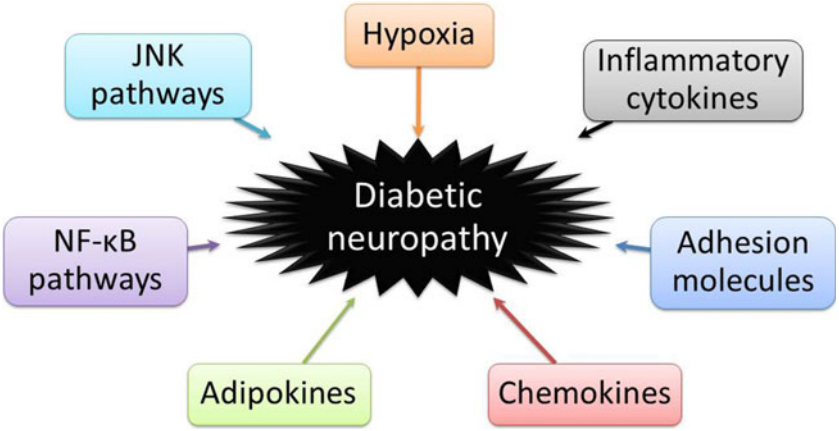

Fig. 2 Potential mechanisms involved in the inflammatory response in diabetic neuropathy. *JNK* JUN N-terminal kinase

primarily to both endothelial cell hypertrophy and hyperplasia. Transient increases in the expression of hypoxia-inducible factor-1α in nerves and similar trends in the expression of several hypoxia-inducible factor-1α target genes are also observed [17]. The exposure of normal rats to hypoxic conditions leads to reduced nerve conduction velocity [18]. The block of potassium channels seen in hyperglycemic hypoxia is attributable to intra-axonal acidification by anaerobic glycolysis and may contribute to the pathogenesis of diabetic neuropathy [19]. Neuronal death (apoptosis) is associated with the upregulation of markers associated with DNA damage and aberrant entry into the G1 phase of the cell cycle [20]. Greater impairments of nerve function are observed in the more ischemic legs of diabetic patients, but reversal of hypoxia does not improve nerve function [21].

Receptor for Advanced Glycation End Products

Deletion of receptor for advanced glycation end products (RAGE) in diabetic mice causes greater myelinated fiber densities and conduction velocities subsequent to acute sciatic nerve crush compared to wild-type controls. Reconstitution of diabetic wild-type mice with RAGE-null versus wild-type bone marrow improves axonal regeneration and restoration of function. After crush, diabetic RAGE-null mice display higher numbers of invading macrophages with greater M2 polarization in the nerve segments compared to wild-type animals. In vitro, treatment of wild-type bone marrow-derived macrophages with advanced glycation end products (which accumulate in diabetic nerve tissue) increases M1 and decreases M2 gene expression in RAGE-dependent manners [22]. Blockade of RAGE improves axonal regeneration in superimposed acute peripheral nerve injury that is attributable to tissue-damaging inflammatory responses.

TNF-α

TNF-α is a potent proinflammatory cytokine involved in the pathogenesis of diabetic neuropathy. In contrast to retinopathy and nephropathy, the association between TNF-α and neuropathy appears to be stronger than the associations of IL-6 and C-reactive protein with neuropathy [23]. Diabetic TNF-$\alpha^{-/-}$ mice show no evidence of abnormal nerve function compared to non-diabetic mice. A single injection of infliximab to inhibit TNF-α in diabetic TNF-$\alpha^{+/+}$ mice suppresses increased serum TNF-α and ameliorates the electrophysiological and biochemical deficits [24]. Animal models of neuropathic pain have persistently indicated that TNF-α has pivotal roles at both peripheral and central levels of sensitization [25].

IL-1

In db/db type 2 diabetes mice, activated astrocytes in the spine increase IL-1β expression, which may induce *N*-methyl-D-aspartic acid receptor phosphorylation in spinal dorsal horn neurons and enhance pain transmission [26]. TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 levels are increased in the spinal dorsal horns of db/db mice, and these increases are inhibited by anti-high-mobility group box 1 [27]. IL-1β and TNF-α mRNA expression are enhanced in the spinal cords of streptozotocin-diabetic rats [28]. Activation of p38 in spinal microglia increases the synthesis and release of TNF-α, IL-1β, and IL-6 [29]. Glucose-induced IL-1β production involves the NOD-, leucine-rich repeats- and pyrin domain-containing 3 inflammasome [30]. IL-1β induces the production of a wide range of cytokines and chemokines through nuclear factor-kappa B (NF-κB) activation, which is enhanced by free fatty acid-induced activation of Toll-like receptor 2 or Toll-like receptor 4 and leads to the recruitment of macrophages.

IL-6

IL-6, a member of the neuropoietic cytokine family, participates in neural development and has neurotrophic activity. IL-6 is a sensitive marker for diabetic nephropathy that predicts progression and severity of type 1 diabetes [31]. IL-6 improves aspects of small and large nerve fibers in diabetic rats.

The functional benefits of IL-6 are related to increased nerve blood flow via a mechanism that involves endothelium-derived hyperpolarizing factor [32]. Increased levels of IL-6, IL-1, TNF-α, and transforming growth factor-β are correlated with the progression of nerve degeneration in diabetic neuropathy [33]. These proinflammatory cytokines affect glial cells and neurons to set the pathological process of diabetic neuropathy in motion. However, TNF-α and IL-6 may not be involved in the development of diabetic peripheral neuropathic pain [34].

Interferon-γ and IL-10

The interferon-γ and IL-10 genes, but not the TNF-α gene, are associated with peripheral neuropathy in South Indian type 2 diabetic patients. The "high-producer" IL-10 genotype and the "low-producer" interferon-γ genotype may be responsible for the downregulation of the immune responses that lead to inflammation in these circumstances [35]. Interferon-γ plays an obligatory role in the development of neuropathy because interferon-γ deficiency is accompanied by complete protection from disease, and infiltration into the nerves of NOD mice deficient for the co-stimulatory molecule B7-2 is also blocked [36]. IL-10 is upregulated in the early phase of Guillain–Barre syndrome and associated with axonal damage, but interferon-γ is not involved in the pathogenesis of Guillain–Barre syndrome [37].

C-Reactive Protein

There is a strong relationship between C-reactive protein and the impairments observed in diabetic neuropathy [38]. High-sensitivity C-reactive protein is a sensitive marker for diabetic nephropathy that predicts the progression and severity of type 1 diabetics [31]. C-reactive protein levels are higher in type 2 diabetic patients with peripheral neuropathy than those without neuropathy [39, 40]. Diabetic subjects with various grades of diabetic foot ulcers exhibit increased high-sensitivity C-reactive protein levels compared to with diabetic patients without foot ulcers [41]. Reduced C-reactive protein levels may serve as a major predictor of the success of percutaneous transluminal angioplasty in diabetic patients with infected foot ulcers [42]. The measurement of C-reactive protein levels may be valuable for distinguishing between infected and non-infected foot ulcers in subgroups of diabetic patients [43].

Adhesion Molecules

The levels of the adhesion molecules P-selectin, E-selectin, and ICAM-1 are higher at baseline in patients with neuropathy compared to non-neuropathic patients [44]. Diabetic peripheral neuropathy patients have higher ICAM-1 levels [45]. Poorly controlled type 2 diabetes patients have higher sE-selectin and soluble vascular cell adhesion molecule-1 levels [46]. Along with P-selectin, the levels of soluble ICAM-1 are higher in patients with neuropathy compared to those with no complications, and these levels correlate with nerve conduction velocities and vibration perception thresholds [47]. Painful neuropathy patients have higher serum level of sE-selectin [33]. ICAM-1 expression is upregulated in diverse zones of the cerebrum and cerebellum of diabetic rats [48].

Chemokines

Chemokines have a crucial role in the infiltration of tissue by immune cells in type 2 diabetes. Regarding the CXC family of chemokines, serum CXCL1 levels are higher in patients with demyelinating forms of diabetic neuropathy [49]. In B7-2-deficient NOD mice that have developed spontaneous autoimmune polyneuropathy, CXCL10 mRNA levels are increased in the sciatic nerve [50]. Members of the CC family of chemokines, which includes CCL2 [50, 51], CCL5 [52], CCL3, and CCL20 [51, 53], are increased in diabetic ZDF rats.

Adipokines

Adipokines are produced mainly or exclusively by adipocytes and have potential immunomodulatory effects. Neuropathic diabetic patients have higher serum levels of leptin and TNF-α [33], and plasma TNF-α affects nerve function [54]. Only sensory conduction velocities are related to TNF-α and leptin concentrations. Diabetic subjects with a diabetic foot exhibit higher plasma IL-6 and resistin levels and lower plasma adiponectin level than diabetics without a diabetic foot. Adiponectin and neuropathy are negatively correlated, and IL-6 and resistin are positively correlated with neuropathy [55]. Serum leptin levels are higher in women with neuropathy than in women without neuropathy, and leptin levels correlate with the degree of neuropathy in subjects with diabetes [56]. Leptin-deficient ob/ob mice develop both large motor and sensory fiber peripheral diabetic neuropathy and small sensory fiber peripheral diabetic neuropathy and respond to pathogenetic treatments [57].

The NF-κB and JNK Pathways

In streptozotocin-diabetic rats with neuropathy, the expressions of NF-κB, IκB-α, and phosphorylated IκB-α are elevated in the sciatic nerve as are the nuclear translocation of the p65/p50 subunit and the levels of TNF-α, IL-6, iNOS, and cyclooxygenase-2 (COX-2) [58, 59]. In liver, adipose, muscle, and hypothalamic tissues, IKKβ–NF-κB activation affects insulin resistance indirectly through changes in body weight, as opposed to the more direct effects on insulin resistance that result from the activation of this pathway in the liver, adipose tissue, and leukocytes. NF-κB is also activated in islet β cells through the actions of glucose and IL-1β, and inhibition of

NF-κB protects β cells from various insults. The NF-κB and JUN N-terminal kinase (JNK) pathways are thus activated in multiple tissues in type 2 diabetes and have central roles in promoting tissue inflammation [60]. Accordingly, reducing the activity of these pathways may be therapeutically beneficial.

Reducing Inflammation as a New Therapeutic Strategy

The immense physical, psychological, and economic costs of diabetic neuropathy underscore the need for causally targeted therapies. The Diabetes Control and Complications Trial for type 1 diabetes showed the importance of early, intensive glucose control in the prevention of complications of diabetes, including neuropathy, and these conclusions were underscored by the subsequent Epidemiology of Diabetes and its Complications [61]. The UK Prospective Diabetes Study showed that intensive control of glycemia is associated with increases in severe myocardial events and is not recommended as standard care for type 2 diabetes [62]. Pain is the most severe consequence of neuropathy in terms of patient quality of life, yet pain remains undertreated. In addition, pain therapies remain variable, and only one third of patients report at least a 50 % reduction in pain with therapy [63].

A selection of the most promising strategies and a summary of compounds in development were provided by a recent review [4]. Most clinical trials have produced disappointing results, but these trials have often been confounded by high rates of improvement in the placebo group or other unanticipated effects [64]. Furthermore, the failures of new drugs in the long term are probably the results of the multiple mechanisms that contribute to neuronal injury in diabetes. Inflammatory mechanisms may have a central role in neuropathy. Therefore, we predict that successful treatment or prevention of diabetic neuropathy will require the prevention of inflammation at the systemic and cellular levels. Consistent with the supposition that inflammation has a key role in diabetic neuropathy, sciatic and sural nerve blood flows and conduction velocities are protected by the anti-inflammatory effects of erythropoietin in diabetic rats [65]. Activation of receptor-mediated inflammatory signaling by advanced glycation end products and oxidized lipoproteins [66] leads to oxidative and nitrosative stress, which can cause microvascular disease. The therapeutic drugs, and the targets of those drugs, that are used to treat diabetic neuropathy by reducing inflammation are shown in Table 1.

NF-κB Inhibitors

In rats with diabetic neuropathy, melatonin improves motor nerve conduction velocities and nerve blood flow, reduces the elevated expression of NF-κB, IκB-α, and phosphorylated IκB-α, and reduces the elevated levels of proinflammatory cytokines (TNF-α and IL-6), iNOS, and COX-2 in sciatic nerves [58, 67]. JSH-23 reverses nerve conduction and nerve blood flow deficits and partially corrects reductions in mechanical pain thresholds. JSH-23 inhibits protein expression of nuclear translocation of p65/p50 subunit and lowers the elevated IL-6, TNF-α, COX-2, and iNOS levels/expression in the sciatic nerve [59]. Inhibition of NF-κB by JSH-23 partially reverses the functional, behavioral, and biochemical deficits that accompany diabetic neuropathy.

p38 MAPK Inhibitors

The pain pathways in diabetic neuropathy involve the inflammatory mediator p38 mitogen-activated protein kinase (MAPK). Recent clinical trials of a novel p38 MAPK inhibitor produce rapid relief of neuropathic pain and decreased systemic inflammation [68]. However, extended treatment with a different p38 MAPK inhibitor does not effectively block systemic or chronic inflammation in patients with rheumatoid arthritis [69]. These results suggest that the role of this kinase in cellular inflammation is complex.

COX-2 Enzyme Inhibitors

Upregulation of the activity of the COX-2 pathway has been implicated in the pathogenesis of diabetic neuropathy. Selective inhibition of the proinflammatory enzyme COX-2 prevents cardiac autonomic neuropathy in type 1 diabetic mice [70], which provides further support for the use of anti-inflammatory agents to prevent neuropathy. Diabetic COX-2-deficient mice are protected against the functional and biochemical deficits of experimental diabetic peripheral neuropathy and protected against nerve fiber loss. In diabetic rats, selective COX-2 inhibition replicates this protection [71], which suggests that selective COX-2 inhibition is beneficial for diabetic neuropathy.

Transient Receptor Potential Vanilloid 1 Agonists

Streptozotocin directly induces its effects through the expression and function of the transient receptor potential vanilloid 1 (TRPV1) channel in sensory neurons and results in thermal hyperalgesia even in non-diabetic streptozotocin-treated mice. A proportion of streptozotocin-treated rats are normoglycemic but still exhibit thermal hyperalgesia and mechanical allodynia. Streptozotocin causes microglial activation, increases TRPV1 expression in the spinal dorsal horn, and increases levels of proinflammatory mediators (IL-1α, IL-6, and TNF-α) in spinal cord tissue. Capsaicin-stimulated release of the calcitonin gene-related peptide is elevated in the spinal cords of streptozotocin-treated animals. Intrathecal administration of resiniferatoxin, a potent TRPV1 agonist,

Table 1 Therapeutic drugs and targets for the reduction of inflammation to treat diabetic neuropathy

Target	Drug	Model, species, and dose	Effects	References
1. NF-κB inhibitor	Melatonin	Two-week treatment at 3 or 10 mg/kg in streptozotocin-induced diabetic rats	Improves motor nerve conduction velocity and nerve blood flow, reduces the elevated expression of NF-κB, IκB-α, and phosphorylated IκB-α, reduces the elevated levels of proinflammatory cytokines.	[58, 67]
	JSH-23	Two-week treatment at 1 or 3 mg/kg in rats 6 weeks after the induction of diabetes with streptozotocin	Reverses nerve conduction and nerve blood flow deficits, partially corrects reductions in mechanical pain thresholds, inhibits protein expression of nuclear translocation of p65/p50 subunit and lowers elevated IL-6, TNF-α, COX-2, and iNOS levels in the sciatic nerve.	[59]
2. p38 MAPK inhibitor	Dilmapimod (SB-681323)	14-day treatment at 15 mg/day in neuropathic pain clinical trials	Rapid pain relief with decreased systemic inflammation.	[68]
	SCIO-469	24-week treatment with either 30 or 60 mg three times daily or 100 mg once daily in patients with active rheumatoid arthritis	Does not effectively block systemic or chronic inflammation.	[69]
3. Selective/ COX-2 inhibitor		Administered after 6 months in diabetic COX-2-deficient mice	Protects against the functional and biochemical deficits of experimental diabetic peripheral neuropathy and against nerve fiber loss; prevents cardiac autonomic neuropathy.	[70, 71]
4. Transient receptor potential vanilloid 1 agonist	Resiniferatoxin	A single dose at 2 μg/kg (intrathecal) in streptozotocin-induced mice/rats	Attenuates thermal hyperalgesia; prevents increases in TRPV1-mediated neuropeptide release in spinal cord tissue.	[72]
5. Anti-inflammatory mesenchymal stem cells	Optimized mesenchymal stem cells	Intraperitoneal injection of $0.5–1\times10^6$ cells in 0.5 ml of Hanks' Balanced Salt Solution per mouse in mice with painful diabetic peripheral neuropathy	Improves thermal hyperalgesia and mechanical pain thresholds; decreases serum levels of many proinflammatory cytokines.	[73]
6. Neuronal nicotinic receptor agonist	A-366833	A single dose at 1, 3, or 6 mg/kg in diabetic neuropathic rats	Exerts antinociceptive activity and attenuates mechanical hyperalgesia.	[74]
7. Microglial activation inhibitor	Minocycline	Two-week treatment at 40 or 80 mg/kg (i.p.) in diabetic neuropathy rats	Attenuates the development of diabetic neuropathy; reduces the levels of IL-1β, TNF-α, lipid peroxidation, and nitrite; improves antioxidant defense in the spinal cords of rats.	[75]
	Minocycline	A single dose or a 7-day treatment at 30 or 100 mg/kg (i.p.) in mononeuropathic rats	Has no effect on acute peritoneal inflammation, or nociception; pre-treatment with minocycline attenuates and delays the development of neuropathic pain.	[76]
	Minocyclineinocycline	/	Prevents the release of proinflammatory cytokines and the development of neuropathic pain.	[28]
8. Cartilage oligomeric matrix protein-Angiopoietin-1		21-day treatment at 100 ng/ml (i.p.) in ob/ob mice	Recovers molecular biomarkers of neuropathy, promotes angiogenesis and suppresses inflammation in the sciatic nerve.	[77]
9. Dipeptidyl peptidase IV inhibitor	PKF275-055, a vildagliptin analog	Six or 11-week administration at 3 mg/kg in streptozotocin-induced diabetic neuropathy rats	Improves body and muscle weight and oral glucose tolerance; counteracts alterations in Na/K-ATPase activity, nerve conduction velocity, and nociceptive thresholds.	[78]

Table 1 (continued)

Target	Drug	Model, species, and dose	Effects	References
10. Nonsteroidal anti-inflammatory agent	Ibuprofen and sulindac	Eight-week treatment with ibuprofen (600 mg 4 times a day) and sulindac (200 mg twice a day) in diabetic neuropathy patients	Positive results even after the onset of diabetic neuropathy.	[79]
11. Flavonoids	Genistein	Five-week treatment at 6 mg/kg in mice with mononeuropathy induced by chronic constriction injury of the sciatic nerve	Reverts neuropathic pain symptoms and the over-expression of IL-1β, IL-6; reverts increases in proinflammation cytokine levels in the sciatic nerve.	[80, 81]
	Baicalein	Four-week treatment at 40 or 80 mg/kg in streptozotocin-induced diabetic mice	Alleviates nerve conduction deficits and small sensory nerve fiber dysfunction; counteracts diabetes-associated p38 MAPK phosphorylation, oxidative-nitrosative stress, and 12/15-lipoxygenase overexpression and activation.	[83]
	Naringin	Four-week treatment at 30 mg/kg (i.p.) in streptozotocin-induced diabetic mice	Attenuates decreases in nociceptive thresholds; is an endogenous antioxidant and membrane-bound inorganic phosphate enzyme; dose-dependently decreases elevations in oxidative-nitrosative stress, inflammatory mediators, and apoptosis in neural cells.	[82]
12. Antioxidant	Coenzyme Q10	Twenty-four day treatment at 50, 100, or 150 mg/kg in diabetic mice	Prevents neuropathic pain development; dose-dependently inhibits mechanical allodynia and thermal hyperalgesia; decreases lipid peroxidation in the dorsal root ganglia, sciatic nerve, and spinal cord; reduces the proinflammatory factors in the peripheral and central nervous systems.	[84]
	Aqueous extract of *Emblica officinalis*	Four-week treatment at 250, 500, or 1,000 mg/kg in diabetic rats	Improves decreased tail-flick latencies, paw withdrawal thresholds, and nociceptive thresholds; attenuates increases in oxidative stress and nitrite and cytokine levels (TNF-α, IL-1β, and TGF-β1) both in the serum and the sciatic nerve.	[85]
	Metanx	Four-week treatment at 4.87 mg/kg or 24.35 mg/kg by oral gavage two times a day in 15-week-old ZDF rats, a model of type 2 diabetes	Alleviates hind limb digital sensory dysfunction, nerve conduction slowing and thermal and mechanical hypoalgesia in the absence of any reduction of hyperglycemia; low-doses increases intraepidermal nerve fiber density; counteracts endothelial nitric oxide synthase uncoupling, inducible nitric oxide synthase upregulation, and methylglyoxal-derived AGEs, nitrotyrosine, and nitrite/nitrate accumulation in peripheral nerves.	[86]

attenuates thermal hyperalgesia but not mechanical allodynia and also prevents increases in TRPV1-mediated neuropeptide release in spinal cord tissues [72].

Anti-inflammatory Mesenchymal Stem Cells

Anti-inflammatory mesenchymal stem cells are prepared with optimized for the anti-inflammatory effects of mesenchymal stem cells. Anti-inflammatory mesenchymal stem cell-treated mice show improvement in radiant heat assays and mechanical stimuli tests and exhibit lower serum levels of many proinflammatory cytokines compared to vehicle- and mesenchymal stem cell-treated groups [73]. Thus, anti-inflammatory mesenchymal stem cell-based therapy represents a new anti-inflammatory treatment that should be considered for the management of the painful diabetic peripheral neuropathy that is induced by streptozotocin.

Neuronal Nicotinic Receptor Agonists

Compounds that act at nicotinic acetylcholine receptors have antinociceptive activities. Among these compounds, tebanicline (a potent nicotinic acetylcholine receptor agonist) has demonstrated analgesic effects across a broad range of

preclinical models of nociceptive and neuropathic pain. Another nicotinic acetylcholine receptor agonist, A-366833 (at 1, 3, or 6 mg/kg) exerts antinociceptive activity and reduces mechanical hyperalgesia in diabetes-induced neuropathic models. A-366833 dose dependently attenuates mechanical hyperalgesia in the complete Freund's adjuvant-induced inflammatory pain model [74].

Microglial Activation Inhibitors

Both neuronal cells and non-neuronal cells, particularly microglia, have roles in the development of neuronal hypersensitivity. Minocycline, a selective inhibitor of microglial activation, attenuates the development of diabetic neuropathy (as measured by cold allodynia and thermal and chemical hyperalgesia), reduces IL-1β, TNF-α, lipid peroxidation, and nitrite levels, and improves antioxidant defense in the spinal cords of rats [75]. The beneficial effects of minocycline are partly mediated by its anti-inflammatory effects (which are the result of reductions in the levels of proinflammatory cytokines) and partly mediated by its modulation of oxidative and nitrosative stress in the spinal cord; these latter modulatory effects might be involved in minocycline's ability to attenuate the development of behavioral hypersensitivity in diabetic rats. Minocycline has no effects on acute peritoneal inflammation or nociception, and the chronic administration of minocycline before peripheral nerve injury attenuates and delays the development of neuropathic pain [76]. Minocyclineinocycline, an inhibitor of microglial activation, inhibits the development of neuropathic pain by preventing the release of proinflammatory cytokines [28].

Cartilage Oligomeric Matrix Protein-Angiopoietin-1

In leptin-deficient ob/ob mice, cartilage oligomeric matrix protein-angiopoietin-1 reduces fasting blood glucose and plasma cholesterol concentrations, upregulates neurofilament 68 and growth-associated protein 43 expression, improves the expression of gap junction proteins (including connexin 32 and 26), suppresses TNF-α and connexin 43 expression, decreases macrophage and T cell infiltration into the sciatic nerve, regenerates small-diameter endoneural microvessels, and increases the phosphorylation of Akt and p38 MAPK upon stimulation of the angiopoietin receptor Tie-2 [77].

Dipeptidyl Peptidase IV Inhibitors

PKF275-055 is a novel, selective, potent, orally bioavailable, and long-acting dipeptidyl peptidase IV inhibitor. PKF275-055 improves body and muscle weight, and glucose metabolism under prevention, protection, and treatment schedules for diabetic neuropathy in streptozotocin-induced diabetic rats. When tested in prevention and protection experiments, PKF275-055 completely prevents decreases in Na/K-ATPase activity and partially counteracts the nerve conduction velocity deficits that are observed in untreated diabetic rats, but has no effects on abnormal mechanical or thermal sensitivity. Therapeutic treatment with PKF275-055 corrects the alterations in Na/K-ATPase activity and nerve conduction velocity that are present in untreated diabetics. PKF275-055 treatment increases mechanical sensitivity thresholds by approximately 50 % and progressively improves alterations in thermal responsiveness. PKF275-055 has an anabolic effect, improves oral glucose tolerance, and counteracts the alterations in Na/K-ATPase activity, nerve conduction velocity, and nociceptive thresholds observed in diabetic rats [78].

Nonsteroidal Anti-inflammatory Agents

A study of 18 male outpatients compares the efficacies of the nonsteroidal anti-inflammatory drugs ibuprofen and sulindac in the treatment of painful diabetic peripheral neuropathy. In this study, discomfort is characterized and rated with a subjective neuropathy score. The responses to both ibuprofen and sulindac are better than the response to placebo across the entire group. There are no changes in glucose control or renal function [79].

Flavonoids

Phytoestrogen has immunomodulatory and anti-inflammatory activities because it reduces the peripheral and central overactivations of NF-κB, the nitric oxide system, and proinflammatory cytokines. In a mouse model of mononeuropathy induced by chronic constriction injury of the sciatic nerve, genistein prevents both neuropathic pain symptoms and the overexpression of IL-1β and IL-6 in the sciatic nerve, dorsal root ganglia, and spinal cord [80]. Genistein prevents increases of TNF-α, IL-1β, and IL-6 in mice with diabetic neuropathy [81]. Naringin is a flavanone with potential antioxidant, antiapoptotic, and disease-modifying properties that are mediated via the modulation of endogenous biomarkers that inhibit diabetes-induced neuropathic pain [82]. Baicalein alleviates nerve conduction deficits and small sensory nerve fiber dysfunction but does not affect diabetic hyperglycemia. Baicalein also counteracts diabetes-associated p38 MAPK phosphorylation, oxidative-nitrosative stress, and 12/15-lipoxygenase overexpression and activation but does not affect intraepidermal nerve fiber loss or the accumulation of glucose and sorbitol pathway intermediates in diabetic mice [83].

Antioxidants

The antioxidant coenzyme Q10 (CoQ10) inhibits body weight loss in diabetic mice but does not affect blood glucose levels.

Low dose and long-term administration of CoQ10 prevent the development of neuropathic pain. CoQ10 inhibits mechanical allodynia and thermal hyperalgesia in diabetic mice in a dose-dependent manner. CoQ10 decreases lipid peroxidation in dorsal root ganglia, sciatic nerve, and spinal cord tissues of diabetic mice. CoQ10 reduces proinflammatory factor levels in the peripheral and central nervous system [84]. These results suggest that CoQ10 may be a low-risk and high-reward drug for protection against diabetic neuropathic pain due to its abilities to inhibit oxidative stress and reduce inflammation through the downregulation of proinflammatory factors.

Emblica officinalis (a potent natural antioxidant) aqueous extract dose-dependently attenuates decreases in tail-flick latency and paw withdrawal thresholds and dose-dependently attenuates increases in oxidative stress, nitrite levels and cytokine levels (TNF-α, IL-1β, and TGF-β1) both in the serum and sciatic nerves of diabetic rats. Insulin, in combination with *E. officinalis* extract, attenuates the diabetic condition and reverses neuropathic pain through modulation of oxidative-nitrosative stress [85]. Metanx, a product containing L-methylfolate, pyridoxal 5′-phosphate, and methylcobalamin (for the management of endothelial dysfunction) increase intraepidermal nerve fiber density and improve multiple parameters of peripheral nerve function in ZDF rats [86].

Conclusions

Inhibition of the inflammatory response is effective in the prevention of diabetic neuropathy. The mechanism by which the inflammatory cascade is initiated and maintained in diabetic neuropathy is currently unknown as are the individual roles of inflammatory molecules in diabetic neuropathy. Common downstream mechanisms of inflammation in diabetic neuropathy include the activation of the NF-κB and JNK pathways and cytokine and chemokine release. These downstream mechanisms lead to the recruitment of immune cells. Inflammatory molecules have redundant functions because many of these molecules cause the activation of similar downstream targets such as NF-κB and several chemokines that share the same receptor. It is important to understand the changes in the inflammatory cascade that occur after blocking an individual inflammatory molecule and to select several candidates for combination therapy. Alternatively, drugs targeting several mechanisms may be more efficient than those that target a single mechanism.

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