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Review

Mechanisms associated with diabetic peripheral neuralgia and potential interventions

Yudie Du [1,#], He Xiao [2,#], Xinting Huang [3], Yiming Shao [3], Ke Song [4,*]

1 Department of Stomatology, North Sichuan Medical College, Nanchong, Sichuan, China

2 Department of Anesthesiology, North Sichuan Medical College, Nanchong, Sichuan, China

3 Department of Clinical Medicine, North Sichuan Medical College, Nanchong, Sichuan, China

4 West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

# Contributed equally

* Corresponding author(s):
Ke Song, songke0408@126.com

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Abstract: Diabetes mellitus (DM), the most prevalent metabolic disorder globally, has been extensively investigated due to its significant clinical implications. Among its most common complications is diabetic peripheral neuropathy (DPN), which predominantly manifests as bilateral limb pain, numbness, and paresthesia. In advanced cases, DPN may progress to foot ulceration and potentially necessitate limb amputation. The precise etiology and pathogenesis of diabetic neuropathy remain incompletely understood; however, sustained hyperglycemia, dysregulated lipid metabolism, and impaired insulin signaling are recognized as key triggers for the cascade of pathophysiological alterations in DPN. Under these metabolic disturbances, the peripheral nervous system's structural and functional integrity—encompassing myelinated and unmyelinated axons, neuronal somata, neurovascular units, and glial cells—is progressively undermined. This review synthesizes recent mechanistic advances in DPN research, centering on the sigma-1 receptor's modulatory orchestration, SGC dysfunction and GalCer metabolic dysregulation in DPN pathogenesis, inhibition of neuroinflammation and apoptosis by microRNA-146a, nerve damage due to Ca^{2+} overload, and dorsal root ganglia neuronal apoptosis resulting from SFA, and summarize possible interventions based on these mechanisms. A systems-level understanding of how these mechanisms collectively drive neuropathy pathogenesis is critical for advancing both early diagnostic tools and pathway-selective therapeutics.

Keywords: diabetes; diabetic peripheral neuropathy; neuropathy pathogenesis; pathway-selective therapeutics; sigma-1 receptor; MiR-146a; neuroinflammation; calcium overload.

1. Introduction

Diabetic neuropathy (DN) ranks one of the most prevalent chronic sequelae of diabetes mellitus, alongside retinopathy, foot ulcers, and cardiovascular manifestations. This neuropathic disorder can affect both central and peripheral nervous systems, with diabetic peripheral neuropathy (DPN) representing the most common form - epidemiological studies indicate approximately 30% of diabetic patients develop this debilitating condition [1]. The global rise in diabetes prevalence has elevated diabetic peripheral neuropathy (DPN) to a major public health concern. In the United States alone, the annual economic burden of managing painful DPN and its sequelae (including neuropathic ulcers and subsequent amputations) ranges from $4–13 billion, accounting for up to 27% of all direct diabetes-related healthcare expenditures [2].

The most prevalent clinical presentation of diabetic peripheral neuropathy (DPN) is distal symmetric sensory

impairment, characterized by progressive numbness and loss of sensation. Notably, approximately 20% of diabetic patients develop neuropathic pain components, which typically manifest as: spontaneous pain (burning, electric-shock-like, or lancinating), stimulus-evoked phenomena (allodynia, hyperalgesia) and paresthetic sensations (chronic pruritus, tingling) [3]. Furthermore, sustained hyperglycemia and metabolic dysregulation collectively impair immune competence, rendering the body vulnerable to infection. These imperceptible, progressively developing wounds may ultimately become infected, potentially resulting in severe limb complications [4]. Clinical studies consistently demonstrate that DPN has become the predominant factor behind non-traumatic lower limb amputations across high-income regions [5].

Nevertheless, current therapeutic strategies for DPN remain suboptimal despite its significant personal and societal impact. This clinical challenge stems from both the disease's intrinsic heterogeneity and complex pathophysiology, compounded by the limited availability of standardized diagnostic protocols [6]. Thus, deciphering the molecular pathogenesis of DPN will undoubtedly catalyze the development of novel targeted therapies, potentially revolutionizing current treatment paradigms. This review synthesizes current findings from cellular and animal models and physical interventions to elucidate the molecular mechanisms underlying DPN pathogenesis. Understanding these pathways and their interrelationships could facilitate early detection, stratified therapeutic approaches, and prognostic evaluation in clinical practice.

2. The mechanisms of DPN

2.1. Sigma-1 receptor-orchestrated neuromodulation of immune-neural crosstalk during inflammatory paradigms

Schwann cells, the predominant glial cell population in the peripheral nervous system, undergo phenotypic transformation following nerve injury. Transitioning to a reparative identity, these cells exhibit markedly upregulated proliferative capacity and elaborate a pleiotropic repertoire of neurotrophic ligands—prominently glial-derived and brain-derived neurotrophic factors—thereby orchestrating axonal reconstitution. Paradoxically, while these factors promote neuronal survival and growth, they simultaneously induce sensory neuron sensitization, thereby contributing to neuropathic pain pathogenesis [7,8]. Beyond neurotrophins, repair-phase Schwann cells secrete multiple pronociceptive mediators, including adenosine triphosphate (ATP). Released ATP activates purinergic receptors on sensory axons, triggering membrane depolarization and subsequent nociceptive signaling [8]. Following peripheral nerve injury, Schwann cells undergo activation and secrete pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1 (IL-1). These mediators serve dual roles: directly sensitizing peripheral nociceptive neurons and initiating chemotaxis of immune cells including macrophages, T lymphocytes, and mast cells. The assembled immune population subsequently amplifies the inflammatory cascade through additional cytokine release, thereby creating a positive feedback loop that sustains and potentiates nociceptive sensitization [7,8]. Schwann cell activity therefore constitutes a critical mechanism in neuropathic pain pathogenesis. Notably, in uninjured peripheral nerves, these glial cells exhibit robust sigma-1 receptor expression [9,10], and their expression persists unabated following nerve injury, remaining stably upregulated throughout the ensuing Schwann-cell proliferative burst [10].

Chronic pain is associated with peripheral neuroinflammation extending to the dorsal root ganglia (DRG). Satellite glial cells (SGCs), which envelop the somata of primary sensory neurons, represent the earliest responders to neural damage. A key activator of SGCs is ATP, released from neuronal cell bodies during injury-induced nociceptive signaling [11]. After neural injury, mainly neurons but also activated SGCs produce BDNF, which contributes to both axonal regeneration and nociceptive sensitization [12,13]. Once activated, SGCs elaborate TNF, thereby exacerbating the hyper-excitability of sensory neurons [11]. Beyond TNF secretion, activated SGCs release specialized proteases that cleave membrane-bound fractalkine (CX3CL1) from sensory neuron somata, generating its soluble bioactive form [14]. CX3CL1, along with neuron-derived chemokine monocyte chemoattractant protein-1 (CCL-2), serves as a key chemotactic signal promoting macrophage infiltration into the DRG following neuronal injury [7]. Macrophages exhibit a distinct spatial organization within the DRG, forming concentric arrays around injured neuronal somata to establish intimate neuron-immune interfaces [15]. Macrophages secrete pro-inflammatory cytokines (e.g., IL-6) that directly sensitize both contacted sensory neurons and adjacent intact neurons through paracrine signaling. This phenomenon results in secondary hypersensitivity of uninjured neurons within the inflamed DRG microenvironment [7]. T lymphocytes, recruited to the DRG by macrophage-derived chemotactic signals [16], also actively participate in DRG neuroinflammation and play a pivotal role in the pathogenesis of neuropathic pain [17]. In

contrast, neutrophils show negligible recruitment to the DRG following peripheral nerve injury [18], save in those post-traumatic intervals when intraneural inflammation achieves overwhelming predominance [7]. The mechanism is shown in Figure 1.

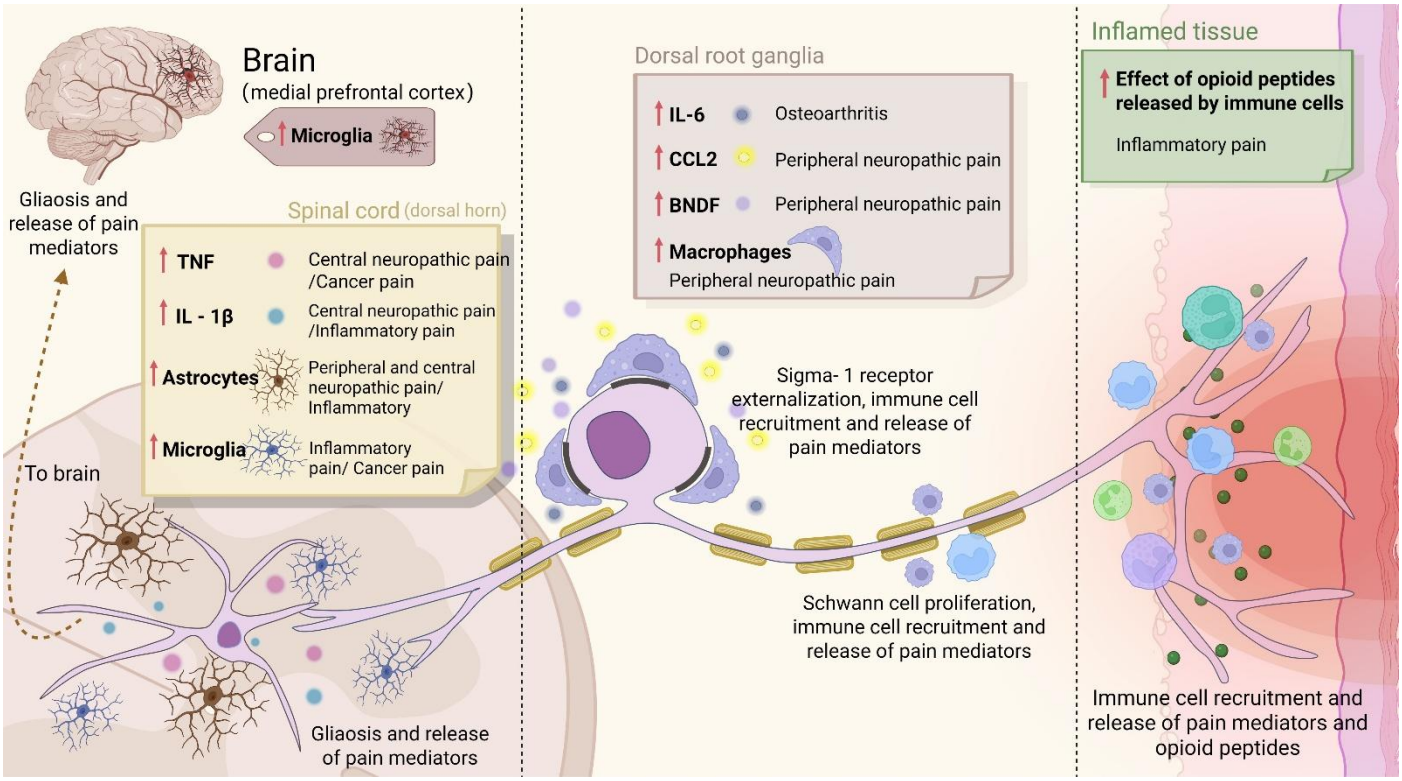

Figure 1. The key role of sigma-1 receptors in the communication between neurons and non-neuronal cells at several key steps in painful neurotransmission. TNF, tumor necrosis factor. IL-6, interleukin-6. BDNF, brain-derived neurotrophic factor. CCL-2, chemokine monocyte chemoattractant protein-1.

Emerging investigations have elucidated the functional significance of sigma-1 receptors in DRG during neuropathic pain states. Notably, sigma-1 expression in DRG neurons substantially exceeds levels found in key central pain-processing regions including the dorsal horn, basolateral amygdala, periaqueductal gray, and rostroventral medulla, suggesting a privileged role in peripheral nociceptive mechanisms [19]. Following peripheral nerve injury, sigma-1 receptors in the somata of affected neurons undergo activation—likely mediated by injury-induced intracellular Ca^{2+} elevation—and subsequently translocate from intracellular compartments to subplasmalemmal regions [18,20]. Experimental studies using sigma-1 receptor knockout mice demonstrated significantly reduced CCL2 production in the DRG, leading to attenuated macrophage infiltration in this peripheral neural tissue [18]. The reduction in macrophage infiltration observed in sigma-1 knockout mice was paralleled by diminished IL-6 levels within the injured DRG, suggesting a coordinated downregulation of pro-inflammatory signaling [18]. Sigma-1 knockout mice show decreased neuropathic sensory hypersensitivity [18,21]. Further investigation is required to elucidate the precise mechanisms by which sigma-1 receptors modulate peripheral neuroinflammatory cascades.

2.2. SGC dysfunction and GalCer metabolic dysregulation in DPN pathogenesis

The pathogenesis of DPN involves multiple interrelated mechanisms, with chronic hyperglycemia, oxidative stress, and sustained inflammatory responses constituting key pathophysiological drivers [22,23]. The aforementioned pathophysiological factors collectively impair the delicate homeostatic equilibrium of the DRG, a critical structure housing sensory neurons and their closely associated SGCs [24]. SGCs are specialized peripheral glia that form intimate structural and functional associations with neuronal somata in the DRG. These cells are essential for neuronal maintenance through multiple mechanisms: precise regulation of perineuronal ion concentrations, neurotransmitter recycling and buffering, and provision of metabolic substrates and immunomodulatory support [25,26]. Recent studies demonstrate that SGCs exhibit significant phenotypic plasticity under pathological stress, actively participating in neuroinflammatory processes and subsequent neuronal impairment [27,28]. Emerging research highlights the

dysregulation of lipid metabolism, particularly sphingolipid pathways, in SGCs under pathological conditions as a pivotal mechanism influencing both glial and neuronal homeostasis. Galactosylceramide (GalCer), a fundamental sphingolipid constituent of both myelin sheaths and neuronal membranes, plays indispensable roles in: preserving structural membrane integrity, enabling efficient signal transduction cascades, and promoting proper myelin assembly and maintenance [29–31]. Impaired GalCer metabolism destabilizes membrane architecture, perturbs essential neuron-glia metabolic coupling, and accelerates neurodegenerative processes in DPN [32]. Xin Xu et al. demonstrate that SGC dysfunction – characterized by lipid metabolic dysregulation and disrupted neuron-glia crosstalk – plays a pivotal role in the pathogenesis of DPN [33]. In 2020, Hanani et al. demonstrated that under pathological conditions, including nerve injury, inflammatory states, and chronic pain, SGCs exhibit marked phenotypic alterations, transforming from quiescent flattened cells to reactive hypertrophic forms. This phenotypic shift is defined by three cardinal features of glial activation in neuropathy: proliferation-induced increases in SGC density, tighter neuronal somata encapsulation, and significant upregulation of glial fibrillary acidic protein (GFAP) expression [27]. The study by Xin Xu et al. provides further experimental validation of these morphological changes in DPN, documenting both substantial proliferation of SGCs populations and marked upregulation of GFAP expression-pathological features indicative of chronic glial activation. This persistent glial reactivity represents a defining characteristic of neuropathic pain syndromes and neuroinflammatory disorders [28]. The enhanced SGC-neuron interactions documented in this study likely represent an initial neuroprotective adaptation to neuronal injury. However, sustained activation progressively dysregulates neuron-glia signaling homeostasis, shifting SGCs from a protective role to a maladaptive state [34–36]. These findings support the prevailing hypothesis that chronic glial activation in neuropathic disorders frequently progresses into persistent neuroinflammation, thereby accelerating neurodegenerative processes and clinical symptom progression [37]. Functional genomic analyses demonstrate that dysregulation of lipid metabolic pathways, especially sphingolipid signaling cascades, plays a pivotal role in mediating SGCs dysfunction during DPN pathogenesis. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses revealed statistically significant enrichment of key lipid regulatory genes, including S1pr3, Sphk1, and Cers2, that modulate sphingolipid signaling cascades and cellular stress response mechanisms [38–40]. These results indicate that SGCs undergo lipid metabolic reprogramming as an adaptive response to pathological metabolic stress. However, the significant decrease in GalCer levels demonstrates the ultimate collapse of these adaptive responses. Moreover, streptozotocin (STZ)-induced overexpression of pyruvate dehydrogenase kinases (PDK2/4) in SGCs, sensory neurons, and recruited macrophages perpetuates a vicious cycle of glial hyperactivation, bioenergetic dysfunction, and chronic neuroinflammation [27,41]. This pathological cascade induces hyperexcitability in sensory neurons, amplifying neuropathic pain while critically impairing neuroglial crosstalk. Notably, the selective loss of lipid metabolism-specialized SGC subpopulations (e.g., Cluster A) reveals subset-specific metabolic vulnerability, resulting in: compromised membrane integrity, disrupted intracellular signaling cascades, and defective myelination processes. Furthermore, GalCer deficiency may disrupt the structural and functional integrity of neuron-SGC interactions, resulting in dysregulated glial activation and amplified neuroinflammatory cascades [42,43]. The dysregulation of GalCer-mediated signaling pathways compromises the ability of SGCs to sustain neuronal homeostasis. This functional alteration transforms SGCs from neuroprotective supporters into pathological contributors, thereby exacerbating neuropathic pain and DRG dysfunction through sustained maladaptive mechanisms [37,42].

2.3. Inhibition of neuroinflammation and apoptosis by microRNA-146a

Emerging research increasingly demonstrates the critical involvement of microRNAs (miRNAs) in the pathogenesis of various neurological disorders [44]. Emerging evidence highlights microRNA-146a (miR-146a) as a particularly significant regulator in neurological disorders, with recent studies consistently demonstrating its critical involvement in disease pathogenesis. MiR-146a serves as a critical modulator of inflammatory responses and innate immune signaling pathways [45–47]. Furthermore, miR-146a exhibits significant dysregulation across multiple inflammation-associated disorders and pathological conditions, with pronounced alterations observed in neural tissues. This consistent pattern underscores its pivotal involvement in neurological disorders, particularly those driven by neuroinflammatory mechanisms [48,49]. Accumulating genetic evidence indicates that miR-146a polymorphisms functionally impair its regulatory capacity, thereby increasing predisposition to various neurological disorders [50,51]. MiR-146a is highly expressed in neuronal, microglial, and astrocytic populations, where it functions as a

critical negative regulator of inflammatory responses through modulation of multiple downstream targets; its regulation of the nuclear factor kappa-B (NF-κB) signaling pathway is the most frequently reported activity [45,47]. The pre-miR-146a transcript is transcriptionally activated by NF-κB, while the mature miR-146a forms a negative feedback loop by post-transcriptionally suppressing key NF-κB pathway components - interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6). This dual regulation mechanism ultimately downregulates NF-κB-mediated proinflammatory cytokine production, including IL-6, IL-8, IL-1β, and tumor necrosis factor-α (TNF-α), which is shown in Figure 2 [45,47]. Upregulation of miR-146a suppresses Toll-like receptor (TLR)-mediated signaling cascades in the cerebrovascular system, thereby attenuating neuroinflammatory responses [52]. Additionally, miR-146a promotes the maturation of rat oligodendrocyte progenitor cells (OPCs) into myelinating oligodendrocytes (OLs) and the neuronal differentiation of neural progenitor cells (NPCs) through targeted downregulation of IRAK1 and TRAF6 expression [53].

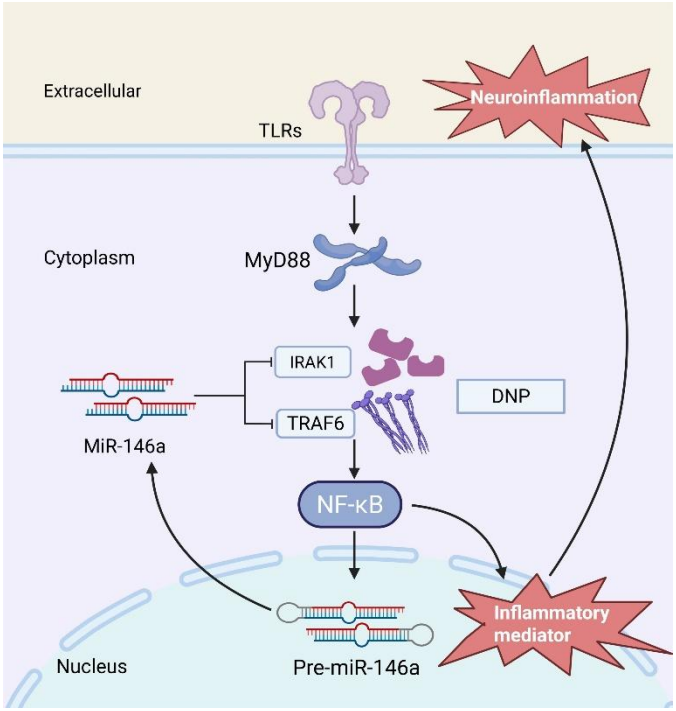

Figure 2. Common neuroinflammatory pathways regulated by miR-146a. IRAK1, interleukin-1 receptor-associated kinase-1. TRAF6, tumor necrosis factor receptor-associated factor 6. TLR, toll-like receptor.

Clinical studies reveal significantly decreased miR-146a expression in serum samples from type 2 diabetes mellitus (T2DM) patients [54], and this downregulation is similarly observed in peripheral nervous system tissues from diabetic animal models, including sciatic nerves and DRG neurons of both mouse and rat models [55–57]. Overexpression of miR-146a attenuates inflammatory responses and reduces apoptosis in Schwann cells under hyperglycemic conditions in rat models, suggesting its potential therapeutic role in mitigating the progression of DPN [58]. In addition, experimental studies demonstrate that miR-146a mimetics effectively mitigate both inflammatory responses and apoptotic cell death in DRG neurons under hyperglycemic conditions [57], promoting axonal growth in neurons by reducing the expression of IRAK1, TRAF6, and thereby alleviating diabetic sensory neuropathy [55]. Current evidence demonstrates that while miR-146a does not substantially lower blood glucose levels in diabetic peripheral neuropathy (DPN) patients, it exerts significant therapeutic effects by modulating key pathological processes—specifically through suppression of neuroinflammation and apoptosis. These findings position miR-146a as a promising disease-modifying target for DPN intervention.

2.4. Nerve damage due to Ca^{2+} overload

Maintaining calcium (Ca^{2+}) homeostasis is essential for proper neuronal physiology, as it regulates three fundamental processes: synaptic vesicle exocytosis for neurotransmitter release, intracellular signaling cascades, and modulation of membrane excitability [59]. Extensive research has established that dysregulation of Ca^{2+} homeostasis plays a pivotal role in both the development of DPN and the generation of diabetic neuropathic pain [60–62]. Dysregulated Ca^{2+} signaling has been consistently observed in neuronal and non-neuronal tissues across both preclinical diabetes models and clinical populations with diabetes [60,63]. Preclinical studies of DPN, utilizing STZ- or alloxan-induced diabetic rat models, demonstrate that sustained elevation of neuronal cytosolic Ca^{2+} levels triggers a cascade of pathological events: neuropathic pain development, mitochondrial impairment, axonal degeneration, and ultimately, neuronal apoptosis [60,63–65]. Chronic hyperglycemia resulting from STZ administration and high-fat/high-sucrose diets induces endoplasmic reticulum (ER) stress and disrupts Ca^{2+} storage in the endoplasmic reticulum [66]. This ER dysfunction leads to pathological Ca^{2+} leakage into the cytosol, a key mechanism driving cytotoxic Ca^{2+} overload within affected cells [66]. And this sustained Ca^{2+} overload disrupts normal neuronal physiology, resulting in pathological hyperexcitability and the development of chronic pain hypersensitivity [66]. STZ-induced diabetes triggers pathological hyperactivation of both T-type (CaV3.2) and L-type (CaV1.2) calcium channels in nociceptive neurons, with particularly pronounced effects in DRG sensory neurons [67,68]. These voltage-gated calcium channels play a critical

role in nociceptive signal transduction. Under diabetic conditions, their pathological hyperactivity facilitates excessive Ca^{2+} influx, resulting in sustained neuronal hyperexcitability and pain hypersensitivity [67,68]. This pathological state manifests through two hallmark electrophysiological alterations: elevated action potential firing frequency and lowered nociceptive thresholds-both central mechanisms underlying the development of mechanical allodynia and thermal hyperalgesia in diabetic neuropathy. Notably, STZ-induced diabetic conditions promote Ca^{2+} overload not only in nociceptive neurons but also in astrocytes [69]. This cascade triggers the secretion of pro-inflammatory cytokines, including TNF-α and IL-6, which subsequently stimulate nociceptive signaling pathways, thereby exacerbating pain perception [69]. Preclinical diabetes models, including STZ-, alloxan-, and high-fat diet-induced systems, consistently demonstrate enhanced microglial reactivity with subsequent overproduction of pro-inflammatory factors. These mediators directly lower neuronal activation thresholds, amplifying nociceptive signaling and perpetuating chronic pain states [70]. Elevated intracellular Ca^{2+} levels in glial cells—especially microglia—trigger pathological activation of pro-inflammatory signaling cascades, ultimately inducing glial cell dysfunction and injury [70].

The Na^{+}/ Ca^{2+} Exchanger (NCX), a transmembrane transporter that regulates intracellular Ca^{2+} homeostasis, represents another critical pathway for Ca^{2+} flux in degenerative disorders and DPN. This antiporter mechanism is essential for maintaining physiological Ca^{2+} concentrations and mediates fundamental processes including excitation-contraction coupling in muscle tissue, intracellular signal transduction cascades and proper neuronal and cardiac function, which is shown in Figure 3 [71]. This transporter functions bidirectionally, mediating the electrogenic exchange of three sodium ions (Na^{+}) for one Ca^{2+} [72] and when operating in reverse mode, it can potentially contribute to pathological intracellular Ca^{2+} accumulation, a mechanism implicated in various disease processes [71]. Under hyperglycemic conditions, this transporter shifts to reverse-mode operation, exacerbating intracellular Ca^{2+} accumulation. This pathological cascade ultimately leads to two critical vascular complications: platelet hyperactivation and glucose-impaired endothelial function [73]. Pharmacological inhibition of the NCX reverse-mode operation (NCXrev) represents a promising therapeutic strategy to mitigate Ca^{2+} overload, prevent excitotoxic neuronal damage, and ultimately alleviate neuropathic pain.

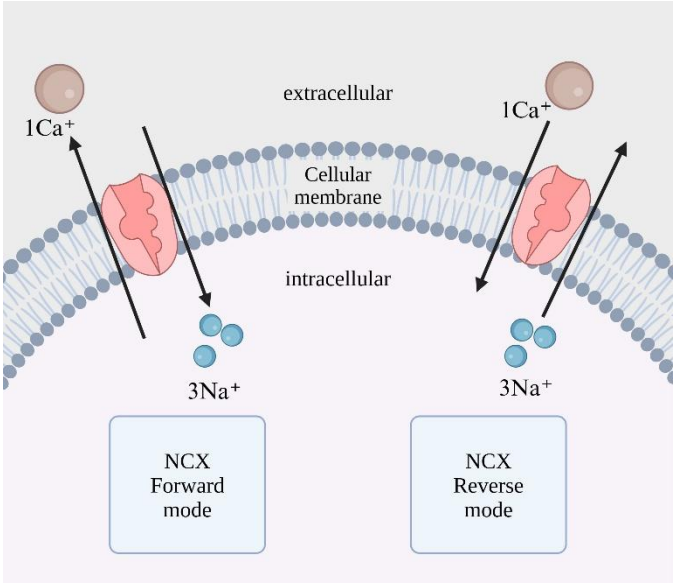

Figure 3. Mechanism of the Na^{+}/Ca^{2+} exchanger. NCX, Na^{+}/Ca^{2+} exchanger.

2.5. DRG neuronal apoptosis resulting from SFA

The development of DPN involves multiple metabolic disturbances, with dyslipidemia playing a central role in disease progression [74]. Patients with T2DM consistently demonstrate elevated circulating levels of saturated free fatty acids (SFAs) compared to healthy controls [75]. SFAs have been consistently shown to promote lipotoxicity [76,77], and trigger apoptotic cell death through multiple molecular pathways [78]. Emerging evidence indicates that the lipotoxic potential of SFAs is critically dependent on their hydrocarbon chain length, which determines the severity of intracellular metabolic dysfunction [79,80]. Ultimately, SFA chain length plays a crucial role in modulating mitochondrial function. Long-chain SFAs damage DRG neurons, where medium-chain SFAs are thought to enhance the function of neurons. Thus, the means by which the SFA chain length affects mitochondrial trafficking, mitochondrial function, and apoptosis were investigated. Long-chain SFAs, including palmitate and stearate, were shown to disrupt mitochondrial function and axonal transport in DRG neurons, ultimately triggering apoptotic pathways. On the other hand, in DRG neurons, shorter-chain SFAs, including myristate and laurate, demonstrated mitochondrial-neutral effects, maintaining normal organelle function and intracellular trafficking without inducing neuronal damage [81].

3. Existing interventions for DPN

3.1. Sig-1R agonists

The activation of the Sig-1R has been demonstrated to alleviate neuroinflammation and downregulate the expression of inflammatory cytokines, specifically TNF-α and IL-1β. Studies have shown that stimulating the Sig-1R with the agonist PRE-084 can reduce oxidative stress in mice suffering from traumatic brain injury. This reduction in oxidative stress leads to decreased activation of microglial cells, which in turn helps to mitigate inflammation [82].

Numerous research studies have highlighted that the anti-inflammatory effects of the Sig-1R are intricately connected to signaling pathways involving key molecules such as the serine/threonine protein kinase AKT, glycogen synthase kinase 3 beta (GSK-3β), and nuclear factor kappa B (NF-κB). NF-κB is widely recognized for its crucial role in both neuroinflammation and neuroprotection [83]. Under normal conditions, NF-κB is primarily located in the cytoplasm. However, upon activation, phosphorylated NF-κB dimers migrate to the nucleus, where they accumulate and subsequently initiate neuroinflammation mediated by microglia [84]. Earlier research has shown that in rats with DPN, there is a substantial increase in the levels of NF-κB in DRG tissues [85]. Moreover, the activation of the Sig-1R has been shown to decrease glutamate accumulation and inhibit inflammatory signaling pathways, such as the NF-κB pathway [86]. Thus, reducing the activation of NF-κB in microglia-like cells could potentially alleviate symptoms of DPN that stem from neuroinflammation. When activated, GSK-3β is a key player in the signaling pathway that works in conjunction with NF-κB [87], thereby promoting the activation of microglia towards a pro-inflammatory state through the stimulation of NF-κB [88]. Additionally, the phosphorylation of AKT at serine 9 results in the inhibition and inactivation of GSK-3β, which is a crucial downstream target of AKT [89]. Research has shown that agonists of the Sig-1R are capable of effectively inhibiting the activity of GSK-3β [90]. Several studies have also suggested that the anti-inflammatory effects of Sig-1R agonists may be attributed to the inhibition of GSK-3β activity [91], thereby supporting the substantial role that GSK-3β plays in anti-inflammatory processes. Detailed mechanism is illustrated in Figure 4.

PRE-084 effectively suppressed the production of pro-inflammatory factors in M1-polarized microglia-like cells. However, its regulatory impact on tissue protection mediated by M2-polarized microglia-like cells warrants further investigation [82].

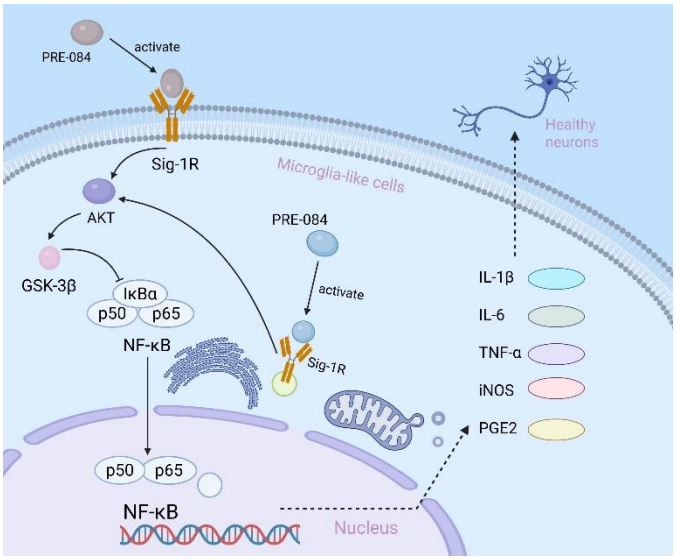

Figure 4. Mechanism of PRE-084 ameliorating pathological neuroinflammation in rats with diabetic neuropathic pain via the AKT/ GSK-3β/NF-κB pathway. Sig-1R, sigma-1 receptor. GSK-3β, glycogen synthase kinase 3 beta. NF-κB, nuclear factor kappa B. TNF-α, tumor necrosis factor-α. iNOS, inducible nitric oxide synthase. PGE2, prostaglandin E2. IL, interleukin.

3.2. Sig-1R antagonists

Sig-1R antagonists have been employed in various rat models of neuropathic pain and may represent a potentially valuable strategy for managing DPN [92,93]. Sig-1R antagonists only alter sensory perception of mechanical and thermal stimuli when there are sensitizing factors present, such as nerve injury [94], making them a promising option for managing neuropathic pain. E-52862 has been identified as a novel selective Sig-1R antagonist that demonstrates effectiveness in both nociceptive and neuropathic pain models [95]. E-52862 is able to cross the blood–brain barrier, bind to the Sig-1R in the central nervous system, and exhibit analgesic effects for neuropathic pain [96]. The antinociceptive effect of E-52862 may be attributed to the normalization of electrophysiological parameters resulting from the blockade of the Sig-1R [93]. However, it is possible that other factors also play a role in the antinociceptive effects of E-52862. E-52862 suppresses spinal wind-up responses that are triggered by the repetitive activation of C-fibers [97]. Another potential contributing factor is that E-52862 has been reported to enhance the descending noradrenaline pain inhibitory pathway [98]. In patients with DPN, E-52862 led to a decrease in pain intensity. However, high placebo response rates may have obscured the distinction between the effects of active treatment and those of placebo [99]. Besides, haloperidol (HAL), a clinically used neuroleptic drug, exerts antiallodynic effects by

antagonizing the Sig-1R receptor. However, it also induces extrapyramidal symptoms [100]. LMH-2, an analog of HAL with high affinity for the Sig-1R receptor, demonstrated dose-dependent antiallodynic and antihyperalgesic effects that were superior to those of gabapentin in mice with chronic hyperglycemia. Importantly, LMH-2 did not induce the extrapyramidal symptoms associated with HAL, highlighting its potential therapeutic value [101].

Sig-1R antagonists may offer therapeutic benefits in addressing both vascular and neural complications in individuals with diabetes [93]. The significance of maintaining adequate perfusion in diabetic neuropathy has been emphasized [102]. Other researchers have also suggested that blocking peripheral Sig-1R can produce an analgesic effect in ischemic pain [103]. The dual effects of Sig-1R antagonists are intriguing, and further research is needed to explore new potential intervention targets for DPN.

3.3. SA-induced reduction in pro-inflammatory cytokine release and concomitant upregulation of miR-146a expression

Recent advances in biomaterial science have yielded numerous innovative materials with potent free radical-scavenging capabilities, demonstrating significant potential for both protecting against diabetic neuropathic damage and slowing the progression of DPN [104–106]. Sodium alginate (SA), a naturally occurring polysaccharide derived from brown algae, is composed of β-D-mannuronic acid (ManA) and α-L-guluronic acid (GulA) [107]. It is a biocompatible, non-toxic biopolymer with versatile applications across multiple industries, including pharmaceuticals, food technology, and cosmetic science [108]. Existing research demonstrates that alginate compounds exhibit significant therapeutic potential through multiple biological mechanisms, including anti-inflammatory, antioxidant, and anti-apoptotic effects, with documented efficacy against neurodegenerative disorders [109], and ischemia-reperfusion cardiac injury [110]. Nema et al. conducted a preclinical investigation evaluating the potential neuroprotective effects of SA in a STZ-induced rat model of DPN [111]. In their work, they found that SA reduced axon demylenation in sciatic nerves of diabetic rats. Meanwhile, after the SA treatment, the diabetic animals exhibited a significantly decreased proinflammatory factors (like IL-1β, IL-6, and TNF-α), caspase-3, oxidative stress levels, and while enhanced the endogenous antioxidant defense systems. Notably, the SA-mediated suppression of proinflammatory cytokine release correlated with upregulated miR-146a expression, suggesting a potential mechanistic pathway for its neuroprotective effects. Recent work by Zhao et al. [112] suggests that SA may suppress NF-κB signaling, potentially attenuating inflammatory responses and oxidative damage in DPN. However, current evidence supporting SA's efficacy as either monotherapy or adjunct treatment for DPN remains limited. Future preclinical studies should prioritize elucidating the precise regulatory mechanisms between SA and miR-146a expression, downstream effects on inflammatory target genes, potential synergistic interactions with existing therapies. To further elucidate the mechanism of action of SA, subsequent investigations should employ immunohistochemistry and Western blot analysis to examine a comprehensive panel of inflammatory and apoptotic proteins.

3.4. The effects of KB-R7943 against DPN

KB-R7943 was originally developed as a selective inhibitor of the NCX, designed to precisely regulate intracellular Ca^{2+} homeostasis in various cell types [72]. This discovery initiative was motivated by the critical need to develop targeted inhibitors of the NCX, given its pivotal role in pathological conditions characterized by Ca^{2+} overload. The research specifically aimed to identify compounds capable of: selective NCX inhibition, minimal off-target effects on other Ca^{2+} regulatory pathways, and preserving physiological ion homeostasis [72]. KB-R7943 has been established as a potent NCX inhibitor that specifically targets the reverse-mode NCXrev, effectively preventing pathological cellular Ca^{2+} overload [67]. While pharmacologic NCX inhibition shows therapeutic promise, it presents a significant clinical challenge due to its dual-edged nature: excessive blockade may induce Ca^{2+} overload in cardiomyocytes [67]. This might cause arrhythmias or cardiac dysfunction. Hence, future research must balance the efficacy of NCX blockers with their safety profile [67].

Recent research focused on testing the effects of KB-R7943 against diabetic neuralgia and related depression [113]. In adult male Wistar rats with STZ-induced diabetes, administration of KB-R7943 (10 mg/kg) demonstrated significant therapeutic effects, including attenuation of mechanical allodynia and reduction of nocifensive behaviors (licking/biting). These effects were comparable to those of amitriptyline, the reference analgesic used in this study. Furthermore, KB-R7943 exhibited neuroprotective properties by partially reversing linezolid-induced sensory axonopathy [114]. Given the established role of the NCX in nociception, these findings indicate that KB-R7943's therapeutic effects are mediated primarily through its selective inhibition of NCXrev activity. By modulating Ca^{2+} homeostasis through this mechanism—along with complementary Ca^{2+}-regulating properties—the compound

effectively prevents pathological Ca^{2+} accumulation and associated neurotoxicity, thereby interrupting key pathways in neuropathic pain development [115]. Although KB-R7943 has demonstrated significant therapeutic potential in preclinical studies, its clinical application remains at a nascent stage. Prior to its broad application in clinical therapy, this compound necessitates further clinical validation to corroborate its target selectivity, refine the potency associated with optimal dosing, and verify its long-term safety profile.

3.5. Effect of exosomes on microglia polarization

In STZ-induced DPN rat models, microglia, the resident immune cells of the central nervous system, exhibited characteristic morphological changes, including cellular hypertrophy, process thickening and progressive retraction of dendritic arborizations [116]. Microglia demonstrate functional polarization into two distinct phenotypes with opposing roles in neuropathic pain: the M1 phenotype, which impairs synaptic neurotransmission and promotes neuropathic pain progression and the M2 phenotype, which excretes neuroprotective cytokines (e.g., IL-10, TGF-β) and attenuates neuropathic pain symptoms [117]. An increased M1/M2 microglial activation ratio has been consistently observed across multiple established neuropathic pain models, including chronic constriction injury (CCI) of peripheral nerves and spinal cord injury paradigms [118,119]. Accumulating evidence indicates that rebalancing the M1/M2 microglial polarization ratio represents a promising therapeutic strategy for neuropathic pain management [120]. The present study demonstrates that M2 macrophage-derived exosomes effectively promote phenotypic switching from pro-inflammatory M1 to anti-inflammatory M2 microglia and significantly ameliorate neuropathic pain symptoms in diabetic rodents, as evidenced by improved mechanical withdrawal thresholds and reduced thermal hypersensitivity [121]. Exosomes, nanoscale extracellular vesicles (30–150 nm diameter) enriched with bioactive lipids, functional proteins, and regulatory microRNAs, have recently gained significant attention as a novel therapeutic platform. [122]. Via a seamless intra vitam–ex vivo pipeline, investigators revealed that M2-macrophage-released nano-vesicles silence the NF-κB cascade—halting p65 and IκBα phosphorylation—while steering microglia into a neuroprotective M2 identity [123], this regulation mechanism ultimately downregulates NF-κB-mediated proinflammatory cytokine production, including IL-6, IL-8, IL-1β, and tumor necrosis factor-α (TNF-α). Nascent investigations have unveiled the capacity of exosomes to assuage neuropathy-induced pain by orchestrating a symphony of anti-inflammatory cues, deploying their molecular cargo of proteins, mature miRNAs, and translatable transcripts to recalibrate the maladaptive neuroinflammatory landscape. [124]. Contemporary studies have validated exosomes as promising nanoscale delivery vehicles for precision gene therapy in pain management, with two demonstrated administration routes: intranasal delivery and intravenous injection. Their therapeutic efficacy stems from two key biophysical properties: low molecular weight (<150 nm diameter) and innate blood-brain barrier (BBB) penetrability [125]. Albeit exosomes shimmer on the therapeutic horizon, their promise is shadowed by an intrinsic heterogeneity—each vesicle a singular mosaic of molecules and biochemical quirks [126]. Compounding this enigma is the acute paucity of robust methodologies to isolate and distil these nano-emissaries, leaving both diagnostic precision and clinical translation suspended in a haze of technical uncertainty. This gap persists despite the fact that most published studies in the field of extracellular vesicles have primarily centered on exosomes. Moreover, exosomes encounter issues like low production yield, contamination, and poor loading efficiency, highlighting the need for additional research [127].

3.6. Physical interventions

For those carrying the quiet chaos of DPN, exercise is not mere motion—it is a polyphonic antidote, re-tuning the fugue of wobble, lost body-whispers, dwindling force, and tardy reflexes into one coherent, weight-bearing cadence [128]. Immersing oneself in a meticulously designed movement curriculum—where sensory re-orchestration, muscular sovereignty, and the twin pillars of anticipatory and reactive postural mastery are simultaneously sculpted—transmutes the fragmented corporeal dialogue of DPN into a symphony of controlled, graceful certainty [129]. Within the quiet crucible of balance training, vestibular whispers, visual echoes, and somatosensory murmurs converge upon the cortical stage, compelling the central nervous system to reconceive its own equilibrium script; through this synaptic renaissance, the brain transmutes fragmentary sensation into an unbroken, sovereign poise that lets the DPN-afflicted body stand as both question and answer in a single, graceful breath [130]. Strength training increases the sensitivity of muscle spindles and improves neuromuscular coordination, which may help compensate for the reduced proprioceptive input resulting from peripheral neuropathy [131]. By summoning vestibular, visual and proprioceptive voices into one commanding chorus, multisystem exercise refines balance from a hesitant gesture into an unspoken certainty, accelerates the cadence of gait, and transfigures pain into a distant echo [131]. Meanwhile, the

rhythmic drum of muscle contraction liberates endorphin auroras and floods micro-vessels with fresh, oxygen-laden tides, weaving an analgesic hush through every step the DPN-affected body dares to take [132].

A sensory neuroprosthesis, worn like a second skin at the ankle, rekindles the phantom orchestra of lost sensation, its targeted pulses whispering forgotten melodies to dulled nerves and reawakening the body's silent symphony of touch and balance [133].For those whose soles had slipped into mute anesthesia and whose every step teetered on the brink of gravity's abyss, the somatosensory neuroprosthesis became a sudden resurrection: silent filaments of current wove themselves into an artificial aura of touch, steadying stance and stride within hours. Beneath this rekindled skin, a deeper alchemy unfolded—nociceptive lightning, once free to race along slender C-fiber highways, found its gates slammed shut by the vigorous drumming of large-diameter afferents, so that pain's shrill anthem was hushed after a single dawn-to-dusk embrace of patterned stimulation [134]. Future inquiry must extend the lens—months, homes, legions of soles—charting durability beyond the first dawn of restored sensation. This would allow for a more comprehensive examination of the clinical outcomes associated with the use of this device over time.

Low-intensity pulsed ultrasound (LIPUS) was firstly proposed as a treatment in mice with DPN [135]. LIPUS silently recalibrates the injured sensorium: mechanical allodynia retreats, thermal withdrawal quickens, and the nerve's erratic voice regains its timbre. By loosening Keap1's grip, it uncages HO-1, flooding the tissue with an endogenous aurora of antioxidant light. This acoustic whisper—no scalpel, no scar—sketches a new therapeutic horizon for DPN, yet the full score of its molecular sonata remains to be written.

4. Conclusions

With the rising global prevalence of diabetes, DPN has emerged as a major health challenge. Significant research efforts have been directed toward understanding its underlying mechanisms to develop effective treatments. Sigma-1 receptors have recently emerged as master integrators of inflammatory dialogue, translating biochemical stress into a synchronized neural-immune semaphore that calibrates host defense without ever quoting the literature, leading to proposed therapeutic strategies involving agonists and antagonists. Additionally, researchers have identified SGC dysfunction and GalCer metabolism as key drivers of DPN progression. Further evidence demonstrates that microRNA-146a suppresses neuroinflammation and apoptosis, while SA reduces pro-inflammatory cytokine release and upregulates miR-146a expression. Another potential mechanism underlying DPN is Ca^{2+} overload-induced nerve damage, which may be mitigated by KB-R7943. Additionally, the therapeutic roles of exosomes and physical interventions warrant further investigation. Given that most current studies are confined to cellular or animal models, future research should prioritize translating these interventions into clinical applications. Despite the proposal of numerous interventions, methodological challenges have prevented many from translating from preliminary research to widespread clinical application. Therefore, future studies must prioritize translating these interventions from bench to bedside.

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