REVIEW ARTICLE

# Neural mechanisms underlying painful diabetic neuropath

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**Abstract:** Painful diabetic neuropathy (PDN), a prevalent complication of diabetes, has become a significant public health concern. It is characterized by nerve damage induced by chronic hyperglycemia, leading to pain, tingling, and numbness, predominantly in the hands and feet. This review comprehensively explores the neural mechanisms underlying PDN, emphasizing the dorsal root ganglion (DRG) as a central hub for pain initiation and transmission. In the periphery, dysregulated pathways in the DRG, including ion channel dysfunction, mitochondrial abnormalities, impaired glucose metabolism, and inflammatory disturbances, contribute to the hyperexcitability of nociceptors and the amplification of pain signals. In the central nervous system, PDN is characterized by structural and functional changes in the spinal dorsal horn and higher brain centers, leading to central sensitization and altered pain processing. The review also highlights the role of epigenetic regulation and emerging insights from single-cell RNA sequencing in understanding PDN. By integrating these peripheral and central mechanisms, future research can focus on developing targeted therapies and multimodal treatment strategies to improve patient outcomes.

**Keywords:** Painful diabetic neuropathy; Diabetes mellitus; Dorsal root ganglia; Spinal cord; Brain.

## INTRODUCTION

Diabetes mellitus, often called diabetes, encompasses a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. As of 2021, there are approximately 529 million individuals living with diabetes worldwide, affecting around 10% of the global population, with the prevalence rising annually. [1-3]. In China, the prevalence of diabetes is 12.8% [4], making it a major public health concern due to its high incidence [5,6]. Among the various complications associated with diabetes, painful diabetic neuropathy (PDN) is one of the most debilitating, affecting approximately one-third of diabetic patients. [7,8]. The healthcare costs related to the treatment of PDN are approximately double those incurred by patients without neuropathy or with non-painful diabetic neuropathy [9]. The prevalence of PDN increases in parallel with the rising prevalence of diabetes [10,11].

Substantial evidence has shown that both the peripheral nervous system (PNS) and the central nervous system (CNS) are critically involved in the pathophysiology of PDN [12]. In this review, we aim to comprehensively examine the neural mechanisms of PDN, integrating insights from the PNS to the CNS. By exploring these interconnected

systems, we aim to provide a framework for understanding PDN pathophysiology and identifying potential therapeutic targets that address both peripheral and central mechanisms.

## PERIPHERAL MECHANISMS OF PDN

Pain perception begins in the dorsal root ganglia (DRG), where nociceptors, specialized sensory neurons, detect noxious stimuli including mechanical injury, extreme temperatures, or chemical irritants [13]. DRG neurons, as pseudo-unipolar cells, connect peripheral tissues such as the skin, muscles, joints, and mucosa with the spinal dorsal horn, where nociceptive signals are relayed to higher CNS center [14,15]. These neurons, lacking protective structures such as the blood-brain barrier and being surrounded by dense blood vessels, are particularly susceptible to toxic circulating substances [16-18]. Chronic hyperglycemia and related metabolic disorders disrupt the normal function of DRG in PDN, leading to structural and functional changes in nociceptors [19-21]. These peripheral mechanisms include biochemical and genetic alterations in DRG neurons and changes in the metabolic and inflammatory microenvironment, all of which collectively contribute to abnormal pain signaling. The following sections delve into these mechanisms, emphasizing the pivotal role of the DRG as a critical interface between peripheral and central pain pathways. The mechanism diagram is shown in Fig. 1.

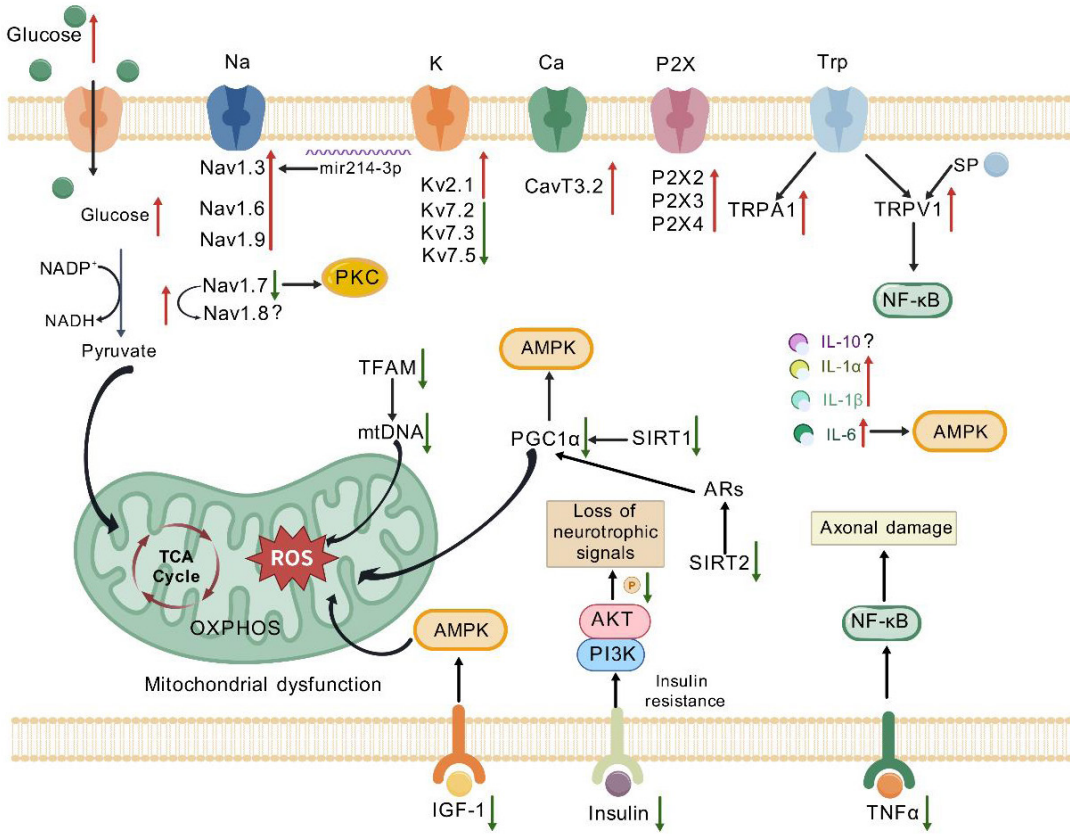


**Figure 1.** Molecular mechanisms of painful diabetic neuropathy in DRG.

Hyperglycemia and insulin signaling disorders induce a variety of molecular impairments in the DRG, leading to the development of neuropathic pain. These impairments include mitochondrial dysfunction, ion channel dysregulation, glucose-metabolism, and inflammation-signal exacerbation. The red arrow represents up-regulation and the green arrow represents down-regulation. NADH, nicotinamide adenine dinucleotide, reduced form; NADP, nicotinamide adenine dinucleotide phosphate; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; AMPK, AMP-activated protein kinase; PKC, protein kinase C; NF-κB, nuclear

factor kappa B; AKT, protein kinase B; PI3K, phosphoinositide 3-kinase; IGF-1, insulin-like growth factor 1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SIRT1, sirtuin 1; SIRT2, sirtuin 2; TFAM, transcription factor A, mitochondrial; TCA cycle, tricarboxylic acid cycle; ROS, reactive oxygen species; SP, substance P; mtDNA, mitochondrial DNA; TNF-α, tumor necrosis factor-alpha. The "p" in the insulin signaling pathway in the figure represents phosphorylation.

## 1. BIOCHEMICAL AND GENETIC FOUNDATIONS OF DRG DYSFUNCTION IN PDN

### 1.1 Biochemical and genetic alterations

Numerous studies utilizing gene chips, tissue sequencing, and multi-omics approaches have demonstrated significant changes in gene and protein expression in the DRG during PDN progression. Transcriptomic analysis of DRG from PDN patients revealed widespread gene expression changes, with 844 differentially expressed genes identified. These include upregulation of inflammation-related transcripts (e.g., macrophage-related genes) and downregulation of neuronal marker genes, implicating intraganglionic inflammation and neuronal loss as pivotal contributors to pain hypersensitivity and nerve dysfunction [22]. In addition, integrated multiomics analyses, including metabolomics, proteomics, and phosphor-proteomics, identified significant reductions in amino acids and phospholipid metabolites essential for cellular maintenance in DRG affected by DPN when compared to healthy controls. These changes were accompanied by extracellular matrix remodeling and alterations in mRNA processing, further supporting the role of metabolic and structural dysregulation in DRG pathology [23]. These findings collectively highlight the intricate interplay between hyperglycemia and genetic regulation in PDN. These alterations span processes such as inflammation, ion channel regulation, sensory loss, and molecular pathways change.

Pain-associated genetic changes in PDN have also been extensively studied. For instance, RNA sequencing of DRG in the type 1 diabetic (T1D) model, an autoimmune condition characterized by insulin deficiency [24], identified 66 differentially expressed transcripts four weeks post-induction, among which several genes were related to hyperalgesia or analgesia, in addition to those linked to inflammation and cell survival [25]. Type 2 diabetes (T2D), which accounts for the majority of cases, is primarily driven by insulin resistance and initial hyperinsulinemia, subsequently, the ability of pancreatic β cells to produce insulin gradually decreases [26]. Proteomic analyses of DRG and sciatic nerve in *db/db* mice which is a T2D model revealed dysregulated metabolic pathways, including reduced glycolysis, tricarboxylic acid cycle (TCA) cycle metabolism, and increased oxidative stress-related proteins. These findings emphasize energetic deficiencies as a key mechanism of neurodegeneration [27]. These proteomic changes interact through multiple pathways, affecting neuronal function and the neural microenvironment, which ultimately leads to the abnormal transmission of pain signals and is closely related to the occurrence and development of pain in PDN. A genome-wide screen of microRNAs (miRNAs) of DRG in a streptozotocin (STZ)-induced diabetic mouse model identified miR-33 and miR-380 as critical regulators of nociceptive hypersensitivity, and miR-124-1 as a mediator of physiological nociception [28]. The studies on pain-associated genetic changes in PDN across different diabetic models uncover multiple underlying mechanisms related to nociception, which can potentially guide the understanding and development of strategies for managing and treating PDN.

Gene expression changes in the DRG appear to be dynamic and correlate with the progression of diabetes. In the STZ-induced diabetic rat model, gene expression studies have shown stage-specific patterns. At one-week post-induction, sensory and motor nerve conduction velocities (NCVs) remain unchanged, while glucose metabolism-related genes are upregulated. At four and eight weeks, NCVs exhibit significant reductions, with extracellular matrix genes downregulated and synaptic vesicle-related genes consistently upregulated across all time points [29]. Notably, the transcriptional changes in late diabetes reflect that DRG is trying to maintain homeostasis despite metabolic stress, which is suggested by altered gene pathways related to cellular stability and regenerative efforts [22]. Similarly, transcriptome analysis showed that the immune pathways of the sciatic nerve and DRG gradually changed at 8,16, and 24 weeks of age in *db/db* diabetic mice. These changes suggest that hyperglycemia-induced nerve damage precedes and drives transcriptional dysregulation over the disease course [30]. The dynamic and region-specific

nature of gene expression alterations underscores the need for stage-specific therapeutic strategies, targeting early sensory and motor nerve conduction deficits and later metabolic disturbances, immune-mediated or structural damage.

Emerging evidence highlights the significant role of epigenetic regulation in PDN. These molecular mechanisms not only influence gene expression but also contribute to the onset and progression of the disease. A study demonstrated alterations in miRNAs patterns, noting that in T1D mice, there is an upregulation of miRNAs-mediated mRNAs processing at cytoplasmic sites (GW/P bodies), accompanied by a downregulation of let-7i and a remarkable increase in miR-341 [31]. RNA sequencing data revealed 11 circular RNAs (circRNAs) and 14 mRNAs significantly correlated with the circRNAs expression profiles in the DRG of the PDN model, with circRNA.4614 being notably upregulated [32]. These findings underscore the intricate epigenetic landscape of DPN, highlighting miRNAs and circRNAs as pivotal regulators of gene expression and potential therapeutic targets for mitigating neuropathic pain.

### 1.2. Mitochondrial dysfunction and oxidative stress

Patients with PDN are often accompanied by systemic hyperglycemia. High levels of glucose and fatty acids in DRG neurons are metabolized through mitochondria. This metabolic process involves transfer of electrons from substrates to produce electron donors such as nicotinamide adenine dinucleotide (NADH), which then transfer electrons along the mitochondrial respiratory chain to drive ATP synthesis via oxidative phosphorylation (OXPHOS) [33]. However, various alterations in DRG mitochondria in PDN patients lead to increased production of reactive oxygen species (ROS) during metabolism. These ROS can inhibit key mitochondrial components, resulting in mitochondrial dysfunction [34]. Proteome analysis of DRG and the sciatic nerve in T2D mice has revealed changes in proteins involved in glutathione metabolism and antioxidant activity[27]. In addition, elevated levels of 3-nitrotyrosine and hydroxyoctadecadienoic acids ( HODEs ) were observed in DRG, which is a marker of protein oxidation and lipid peroxidation [35]. Deep-proteome profiling of the high-fat diet (HFD) -induced PDN models further revealed that proteins related to mitochondrial fission, such as dynamin-related protein 1 (Drp1), mitochondrial fission 1 protein (Fis1), and mitochondrial fission factor (Mff), were significantly upregulated in the DRG. This result suggests that mitochondria in the DRG of these diabetic mice undergo fragmentation and apoptosis at the onset of mechanical pain [36]. Furthermore, levels of proteins related to the TCA cycle and the mitochondrial respiratory chain were decreased in DRG neurons of long-term diabetic rats [37], highlighting that mitochondrial oxidative stress plays an important role in the pathogenesis of PDN.

The role of mitochondrial dysfunction in PDN is further emphasized by the involvement of peroxisome proliferator-activated receptorγcoactivator-1α (PGC-1α), which functions as a co-transcriptional activator that regulates the expression of various mitochondrial proteins [38,39]. PGC-1α and adenosine monophosphate-activated protein kinase (AMPK) signaling were inhibited in DRG of diabetic rodent models [40]. This reduction likely impairs PGC-1α to regulate the mitochondrial environment and scavenge ROS, thereby contributing to the oxidative stress observed in diabetic patients [41,42]. It further suggests that PGC-1α dysfunction weakens the antioxidant defenses in DRG neurons, making them more vulnerable to oxidative damage and exacerbating PDN [43]. In addition to PGC-1α, mitochondrial transcription factor A (TFAM) also plays a crucial role in maintaining mitochondrial function [44]. TFAM enhances mitochondrial DNA expression in peripheral DRG neurons [45,46], and a decrease in both mitochondrial DNA and TFAM levels has been observed in chronic diabetic models. Overexpression of TFAM has been shown to rescue these defects, protecting DRG neurons from oxidative stress [47,48]. This highlights the potential for targeting TFAM expression as a therapeutic approach to mitigate mitochondrial dysfunction in PDN. Furthermore, sirtuins (SIRTs), which are $NAD^+$-dependent enzymes involved in mitochondrial regulation, also contribute to the mitochondrial health of DRG neurons [49]. Activation of the SIRT1-PGC-1α pathway by overexpression of SIRT1 has been shown to protect neurons from DPN injury [50]. Overexpression of SIRT2 enhances polyol pathway activity and promotes the growth of cultured DRG neurons, and the use of aldose reductase inhibitors to increase SIRT2 and PGC-1α expression may provide a strategy to promote neuronal regeneration and mitigate the effects of PDN [51]. Taken together, these findings underscore the

critical role of mitochondrial dysfunction and oxidative stress in the pathophysiology of PDN. The dysregulation of mitochondrial proteins, the downregulation of protective factors such as PGC-1α, TFAM, and sirtuins, and the accumulation of ROS all contribute to neuronal damage and pain hypersensitivity.

### 1.3. Ion channel dysregulation and nociceptor hyperexcitability

Ion channel dysregulation is a fundamental contributor to the hyperexcitability of nociceptors observed in PDN. The increased excitability of sensory neurons directly contributes to the development and maintenance of PDN [52,53]. In particular, the plasticity and activity of ion channels in DRG neurons are crucial for regulating overall cellular excitability and nociceptive signaling [2,54,55]. Key ion channels and receptors implicated in PDN include sodium channels (Nav), potassium channels (K), calcium channels (Cav), transient receptor potential receptors (TRP), and P2X purinergic receptors (P2X). These molecular players collectively shape the pathological sensory responses of PDN.

Sodium Channels (Nav) play a crucial role in the development and maintenance of PDN, making them a key target for understanding the molecular mechanisms underlying this condition. In diabetic neuropathy, alterations in the expression of several Nav isoforms in sensory neurons have been observed, which contribute to the pathophysiology of PDN [56,57]. Specifically, the upregulation of Nav1.3, Nav1.6, and Nav1.9 mRNAs, alongside the downregulation of Nav1.8, is associated with nociceptive sensitization in diabetic models [57]. Overexpression of miR-214-3p attenuates nociceptive sensitization by regulating the expression of Nav1.3 in DRG neurons in an STZ-induced diabetic model [58]. Furthermore, activation of protein kinase C (PKC) in the DRG neurons of diabetic rats increases Nav1.7 phosphorylation, which in turn modulates neural excitability [56]. A functional variant of Nav1.7 has also been identified in patients with idiopathic small fiber nerve neuropathic pain, where it impairs slow inactivation, leading to sustained hyperexcitability of DRG neurons [59]. Notably, Nav1.7 and Nav1.8 work synergistically in DRG neurons. Nav1.7 enhances the stimulus magnitude required to activate Nav1.8, thereby increasing nociceptor sensitivity in diabetic models [55,60]. However, in multiple studies of STZ-induced diabetic rats, the expression of Nav1.8 protein and mRNA has inconsistent results [57,61-63]. The reason for this conflicting result is currently unknown and further studies are needed to validate the alteration.

Potassium Channels (Kv) play a critical role in modulating pain and neuronal excitability [64,65]. In T1D rats, the density of total potassium current, type A current, and delayed rectifier current was markedly diminished in large and medium DRG neurons. Likewise, a significant reduction was observed in the Kv current of small DRG neurons. [66], suggesting a general dysfunction of Kv in diabetic neuropathy. Notably, in late-stage PDN models, high levels of Kv2.1 protein expression have been detected in the DRG [67], indicating a potential compensatory response to nerve injury. Several studies have also reported a decrease in the mRNA and protein levels of Kv7.2, Kv7.3, and Kv7.5 in diabetic rat DRG neurons, along with a reduction in M-current density. These changes are associated with increased neural excitability, which likely contributes to the development of pain hypersensitivity. Such alterations in Kv expression may represent an activity-dependent compensatory mechanism aimed at limiting the hyperexcitability of DRG neurons, a hallmark of neuropathic pain [68,69]. However, the overall reduction in total potassium currents and the specific downregulation of Kv subtypes can lead to prolonged nociceptive signaling, further exacerbating pain responses in diabetic models.

Calcium Channels (Cav) play a key role in the development and progression of neuropathic pain, with their upregulation observed in DRG neurons in rodent models of PDN [70]. Notably, the enhancement of Cav3.2 T-type isoforms in the PDN model contributes to the hyperexcitability of DRG neurons and increased central sensitization to pain [71]. Glycosylation inhibitors have been shown to reduce Cav3.2 T-channel currents in vitro, and in vivo administration of these inhibitors reverses both mechanical and thermal nociceptive sensitization in rodent PDN models [72]. The upregulation of Cav T-channels in DRG neurons during PDN amplifies the transmission of single action potentials from the periphery to the DRG, resulting in the generation of multiple action potentials that reach the spinal cord axons. This cascade amplification effect may play a significant role in the progression of pain throughout different stages of PDN [73]. Furthermore, transcriptome analysis of the PDN model has revealed that glycosyltransferases and sialic acid-modifying

enzymes, which are involved in modifying Cav3.2T function, are impaired in these conditions [74]. Since T-type channels lower the threshold for action potential firing and enhance neuronal excitability, the Cav T-type isoform emerges as a crucial target for PDN treatment [75-77].

Transient Receptor Potential (TRP) Channels are a class of non-selective cation channels that play a critical role in the initiation of pain, and their dysregulation or dysfunction is implicated in the development of PDN [78]. In T1D rats, hydrogen sulfide induces nociceptive hypersensitivity and loss of epidermal fibers by activating TRPV1, TRPA1, and TRPC channels [79]. Early diabetic neuropathy is often characterized by increased TRPV1 activity in DRG neurons [80]. The upregulation of TRPV1 expression is mediated via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway that is activated by α-lipoic acid (ALA) [81]. Activation of the TRPV1 receptor enhances substance P release, triggering mast cell degranulation, impairing skin microcirculation, and leading to sensory neuron apoptosis [82]. Besides, TRPA1 is also notably upregulated in the DRG of diabetic animals [83]. Activation of TRPA1 contributes to the development of pain in PDN [84]. The dysregulation of both TRPV1 and TRPA1 channels significantly contributes to nociceptive hypersensitivity in PDN, highlighting their role in the development and progression of pain.

P2X purinergic receptors are non-selective ligand-gated cation channels that mediate ATP-induced inward currents. These receptors are abundantly expressed in DRG neurons and play a crucial role in the generation and transmission of pain [85,86]. The upregulation of P2X2, P2X3, and P2X2/3 receptors in DRG neurons is associated with the occurrence of abnormal mechanical pain in T1D mice [87]. Notably, the expression of membrane-bound P2X3 receptor protein in DRG was significantly increased in diabetic rats, while the total protein level of the P2X3 receptor remained unchanged. This suggests that P2X3 receptors undergo translocate from the cytoplasm to the cell membrane in PDN models [88,89], where they are more likely to participate in pain signaling. Additionally, the increased expression of P2X4 receptors in DRG neurons from diabetic rats is associated with neurogenic mechanical nociceptive hypersensitivity [90]. This upregulation further emphasizes the role of P2X receptors in amplifying pain transmission under diabetic conditions. Taken together, these findings highlight the importance of P2X receptors, particularly P2X4, in the pathogenesis of pain in diabetic neuropathy, making them potential targets for therapeutic intervention in pain management.

## 2. METABOLIC AND INFLAMMATORY DYSREGULATION

Metabolic and inflammatory disturbances in the DRG under diabetic conditions play a critical role in intensifying neuropathic pain in PDN. Disruption in glucose metabolism caused by sustained high blood glucose levels leads to the accumulation of glucose metabolites, exacerbating insulin resistance and impairing multiple signaling pathways [25,27,91,92]. These metabolic perturbations are pivotal in the onset of peripheral neuropathy and pain. Insulin signaling is critical for sensory neuron function, with its disruption closely linked to PDN development [93-95]. Insulin receptors (IRs) are expressed in DRG neurons and axons [96,97], where they activate downstream pathways, such as the phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) signaling cascade [98], vital for neuronal survival and plasticity. Decreased Akt phosphorylation and impaired synaptic growth in DRG neurons highlight the effect of insulin resistance on nerve injury in *ob/ob* mice [99]. Insulin resistance, a hallmark of T2D, increases DRG neurons' vulnerability to metabolic stress, thereby contributing to neuropathy [100-102]. Similarly, insulin-like growth factor-1 (IGF-1), which shares signaling pathways with insulin [103], plays a neuroprotective role and is implicated in the development of PDN [104-106]. For instance, the decreased expression of IGF-1 in nociceptive DRG neurons of T1D rats mediates neuropathic pain [107]. IGF-1 activates the AMPK pathway, which is critical for mitochondrial function, axon growth, and glycolysis [108,109]. IGF-1 overexpression in the diabetic neuropathy model has been shown to prevent Schwann cells from hyperglycemia-induced apoptosis via the PI3K signaling pathway [110]. In summary, the disruptions in glucose metabolism and insulin signaling along with the roles of insulin resistance and IGF-1 are all integral aspects that significantly influence the development of PDN.

Inflammation plays a significant role in DRG dysfunction during PDN. Transcriptome analysis of PDN patients revealed a significant upregulation of immune-cell marker genes. This included

increased expression of T cells, B cells, and macrophage markers, as well as elevated levels of inflammatory cytokines, such as IL-1α, IL-6, and IL10, though tumor necrosis factor-alpha (TNF-α) expression showed a paradoxical decrease [22]. Similarly, another genomics study demonstrated macrophage recruitment and IL-10 upregulation in both the early and late stages of disease in *db/db* mice, emphasizing the dynamic nature of immune responses during PDN progression [30]. Furthermore, proteomic studies in T1D models corroborated significant alterations in both pro-inflammatory and anti-inflammatory factors within the DRG, suggesting a complex balance between immune activation and resolution during neuropathic pain [25]. In heat shock protein 70 knockout mice, sequencing results identified widespread activation of inflammatory pathways in the DRG, with marked increases in specific pro-inflammatory signals such as CD163, TNFα, and IL-1β [111]. These findings collectively support the notion that elevated levels of pro-inflammatory cytokines may sensitize DRG neurons, amplifying nociceptive signaling and mediating pain development.

Key cytokines such as IL-10, IL-6, and TNF-α play pivotal roles in these processes. IL-10, an anti-inflammatory cytokine widely expressed in DRG neurons [112], is associated with hypoalgesia in neuropathy [113] and may contribute to axon repair and inflammation inhibition [114]. However, decreased IL-10 expression in PDN models and its pain-relieving effects upon recombinant supplementation highlight the complexity of its in inflammation and pain [115]. Conversely, IL-6 induces persistent hyperexcitability in DRG neurons, a process reversible by IL-6 inhibitor, and its pro-inflammatory effects are linked to reduced AMPK activity in PDN [116-118]. TNF-α, another key inflammatory mediator [119], shows differential roles, contributing to acute hypoalgesia [120,121] and axonal damage via the NF-κB pathway in diabetic models [122], while targeted overexpression in DRG has been shown to alleviate T1D-induced pain [123]. In conclusion, these key cytokines have diverse and complex roles in the development of PDN, highlighting the importance of further understanding their functions for potential therapeutic interventions.

## 3. EMERGING INSIGHTS

Recent advances in single-cell RNA sequencing (scRNA-seq) have transformed our understanding of PDN. This technology allows for comprehensive, multidimensional analysis that goes beyond single-pathway approaches, offering unprecedented insights into the cellular and molecular landscapes of the DRG. Over recent years, bioinformatic tools have evolved rapidly, enabling a shift from traditional single-pathway studies to integrative approaches that provide a holistic understanding of the complex mechanisms underlying PDN. Among these advances, scRNA-seq technology has emerged as a powerful tool, offering unprecedented resolution in mapping gene expression within the DRG [124]. Single-cell RNA sequencing has revealed remarkable heterogeneity within the DRG, uncovering novel neuronal subpopulations associated with somatosensory neurons [125,126]. Among these, a newly identified group of neurons, termed MAAC ($Fxyd7^+$/$Atp1b1^+$), was characterized by elevated expression of neurofilament and cytoskeletal-related genes [127]. Fxyd7, a type I membrane protein expressed in the brain, is known to regulate neural excitability [128], while Atp1b1 is a key subunit of the $Na^+/K^+$-ATPase (NKA) complex. Dysregulation of NKA activity has been observed in PDN patients [129], underscoring its relevance in pain mechanisms [130,131]. Similarly, in an HFD mouse model, increased expression of Mas-related G protein-coupled receptor d (Mrgprd) was observed in a DRG subpopulation [132]. Mrgprd activation was linked to enhanced DRG excitability in PDN models. Another intriguing discovery involves Nageotte nodules, neuroma-like structures abundant in the DRG of PDN patients. Spatial transcriptomics revealed high secreted phosphoprotein 1 (SPP1) expression in these nodes, potentially contributing to axonal degeneration and nociception via endoplasmic reticulum stress and extracellular matrix remodeling [23,133]. Targeting SPP1 or its translational regulation, such as through eukaryotic initiation factor 4E (eIF4E) inhibitors, could offer new therapeutic avenues [134-137].

## THE CENTRAL MECHANISM OF PDN

### 1. Changes in the spinal dorsal horn

Peripheral changes in PDN set the stage for the amplification of nociceptive signals. However, pathological changes do not remain confined to the periphery. As nociceptive signals travel through

the spinal cord and ascend to higher brain centers, they undergo further modulation, ultimately contributing to the development of central sensitization and abnormal pain processing in PDN. The central nervous system, including the spinal cord and brain, plays a pivotal role in integrating and amplifying these nociceptive inputs, transforming acute pain into a chronic, debilitating condition [138]. To fully understand the mechanisms of PDN, it is essential to examine how spinal connectivity and brain dysfunction work in concert to exacerbate pain perception and how these central changes interact with peripheral sensitization to maintain chronic pain.

The spinal dorsal horn serves as a critical relay and processing hub for nociceptive inputs from DRG neurons. Aδ and C fibers of DRG neurons terminate in the superficial layer of the dorsal horn, where they connect with projection neurons and interneurons, forming intricate excitatory and inhibitory networks essential for various sensory processing [139-141]. In PDN, enhanced nociceptive input from DRG neurons induces morphological changes in spinal dorsal horn neurons and disrupts spinal cord inhibition circuits, resulting in central sensitization and amplified pain perception [142,143]. For instance, the upregulation of metabotropic glutamate receptor 5 (mGluR5) increases synaptic excitability of spinal dorsal horn neurons, thereby facilitating pain signal transmission [144]. Additionally, rac1 signaling has been shown to remodel dendritic spines in spinal laminae IV-V, heightening spinal neuron sensitivity to DRG inputs and lowering the threshold for mechanical nociceptive pain [143]. Neurotropic factors such as nerve growth factor (NGF) exhibit dynamic expression patterns in the spinal dorsal horn and DRG during PDN, contributing to hyperalgesia and aberrant pain responses [145]. Concurrently, decreased expression of opioid receptors on primary afferent fibers impairs endogenous pain suppression and reduces the efficacy of opioids in the treatment of pain caused by PDN [146]. Glial cells in the spinal cord also play a significant role in pain signal modulation. For example, activated glial cells release brain-derived neurotrophic factor (BDNF), which exacerbates mechanical pain in PDN [147,148]. Furthermore, dysregulation of sodium channels in DRG neurons, along with phosphorylation of the p38 mitogen-activated protein (MAP) kinase pathway in spinal microglia, perpetuates mechanical pain [149].

## 2. Structural and functional changes in the brain

Beyond the spinal cord, dysfunction in higher brain centers also contributes to PDN. Sensory information from the dorsal horn is relayed to the brain via ascending pathways, including the spinothalamic and spinoreticular tracts, which transmit signals to the thalamus, somatosensory cortex [150], and other brain regions involved in pain perception and modulation [151]. PDN is associated with significant structural and functional alterations in higher brain centers. Magnetic resonance imaging (MRI) studies reveal reduced gray matter in the primary somatosensory cortex, supramarginal gyrus, and cingulate cortex in patients with diabetic neuropathy. This reduction is more pronounced in PDN patients compared to those with non-painful diabetic neuropathy, reflecting the impact of chronic pain on cortical structures [152]. Additionally, abnormal neuronal and axonal activity markers have been identified in the dorsolateral prefrontal cortex (DLPFC), highlighting potential disruptions in pain processing circuits [153].

Changes in functional connectivity further emphasize the brain's alteration in pain modulation in PDN. Reduced functional connectivity between the thalamus and cortex manifests as abnormalities in the dorsal and ventral attentional networks, as well as the dorsal anterior cingulate cortex (ACC). These disruptions impair synchronous brain activity, enhancing the processing of pain signals and contributing to heightened pain perception [154,155]. Electrophysiological studies corroborate these findings, showing diminished inhibitory functions in the cerebral cortex of diabetic neuropathy patients [150]. This loss of inhibition may lower the threshold for pain signal amplification, compounding the experience of chronic pain. These data indicate that structural and functional alterations in higher brain centers involved in pain perception and modulation contribute to the development and exacerbation of PDN (Fig. 2).

The abnormal nociceptive input is transmitted from DRG neurons to the spinal dorsal horn, resulting in morphological changes in the spinal cord and affecting the spinal cord's transmission of pain signals to the brain. The ascending pathway of pain starts from the spinal cord, passes through the brainstem, and the midbrain passes upward to the sensory cortex. This process may also lead to the occurrence of complications such as fear,

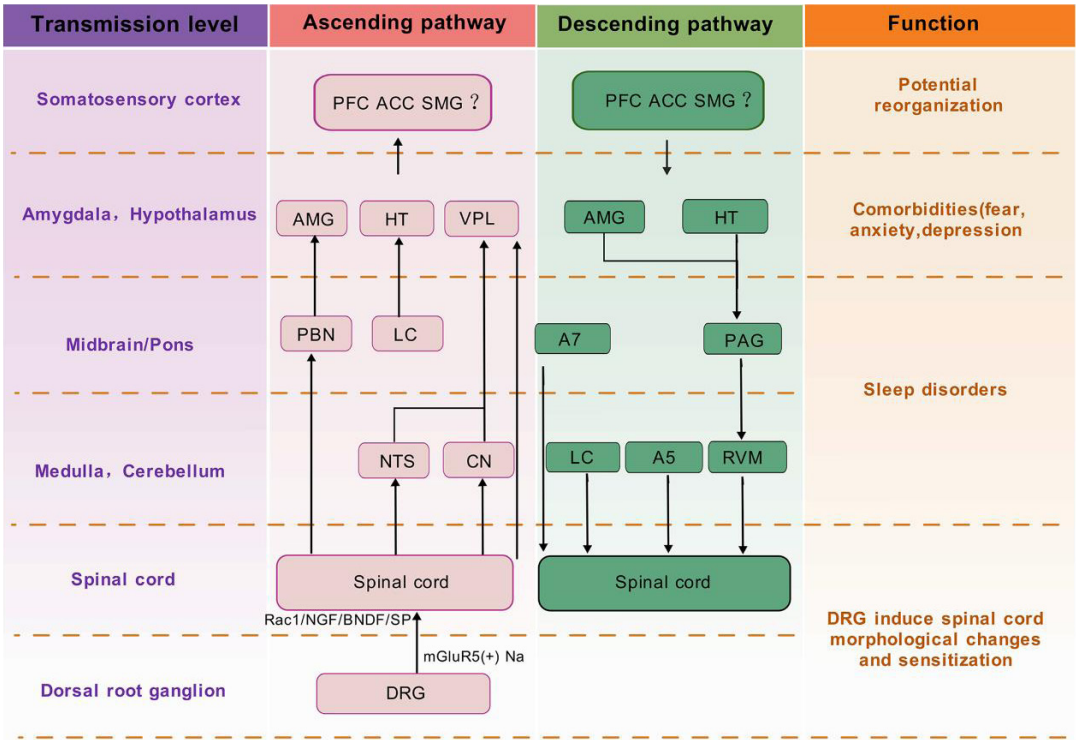


**Figure 2.** Overview of central neural pathways involved in painful diabetic neuropathy.

anxiety, and depression in patients with painful diabetic neuropathy. The descending of PDN from the brain to the spinal cord promotes or inhibits the dysfunction of the pain pathway. The purple box is the transmission level of pain signals, the red box is the ascending pathway, and the green box is the descending pathway. Arrows represent different pain ascending and descending pathways. PFC, prefrontal cortex; ACC, anterior cingulate cortex; SMG, supramarginal gyrus; AMG, amygdala; HT, hypothalamus; VPL, ventral posterolateral nucleus; PBN, parabrachial nucleus; LC, locus coeruleus; NTS, nucleus tractus solitarius; CN, caudate nucleus; A7, noradrenergic cell group A7; A5, noradrenergic cell group A5; PAG, periaqueductal gray; RVM, rostral ventromedial medulla; Rac1, Ras-related C3 botulinum toxin substrate 1; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; SP, substance P. This figure is concluded by referring to two reviews [151,156].

## 3. Dysregulation of pain signal and psychological comorbidities in PDN

Abnormal pain-signal transmission in PDN involves multiple pathways and regions, including the thalamus, periaqueductal gray (PAG), rostral ventromedial medulla (RVM), and cingulate cortex [151]. Changes in thalamic ventral posterolateral (VPL) neurons have been observed in PDN, with increased spontaneous and evoked activity in response to tactile stimuli [157]. These changes in the thalamus are consistent with the enhanced nociceptive input to the spinal dorsal horn, emphasizing the key role of the thalamus in amplifying abnormal pain signals [158]. Studies in diabetic animal models have revealed alterations in descending pain modulation systems, which transmit signals from higher brain centers to the spinal cord. For instance, In PDN models, decreased PAG activation and abnormal rostral ventromedial medulla (RVM) cell activity impair the descending regulation of pain and consequently exacerbate hyperalgesia [159-161]. The balance between nociceptive signal promotion and inhibition is disrupted in PDN, contributing to the development and persistence of neuropathic pain.

Beyond structural and functional changes, PDN is associated with significant psychological comorbidities, including anxiety, depression, and sleep disturbances. Dysregulation of the amygdala, driven by persistent nociceptive input, likely plays a key role in these manifestations [162,163]. Functional MRI studies have highlighted abnormal activity in

regions such as the dorsal anterior cingulate cortex and thalamus, which may mediate the interplay between chronic pain and emotional dysregulation [154]. Additionally, disruptions in brain region connectivity, particularly in the dorsal and ventral attentional networks, contribute to the cognitive and emotional challenges faced by PDN patients [155]. These findings suggest that PDN extends beyond physical pain, profoundly impacting the overall mental well-being of affected individuals.

## CONCLUSIONS

PDN presents a complex clinical challenge, with its prevalence increasing annually alongside the growing global burden of diabetes. This review highlights the pivotal role of the DRG in the pathogenesis of PDN, from peripheral mechanisms to CNS alterations. Emerging evidence underscores the DRG as a crucial hub for pain initiation and transmission, with numerous molecular, cellular, and circuit-level changes contributing to the development and maintenance of neuropathic pain. In the periphery, dysregulated pathways in the DRG, including ion channel dysfunction, impaired glucose metabolism, and mitochondrial abnormalities, have been identified as key contributors to PDN pathogenesis. These insights have paved the way for targeted therapeutic interventions, such as gene therapies, RNA-based treatments, and innovative drug delivery systems using nanotechnology. While most of these strategies remain in preclinical stages, they hold immense potential for improving treatment specificity and reducing systemic side effects. In the CNS, PDN is associated with structural and functional changes, including gray matter reduction, altered neurochemical levels, and dysregulated descending pain modulation pathways. These central changes amplify pain perception and contribute to emotional comorbidities, such as anxiety and depression. Understanding the interplay between peripheral and central mechanisms is critical for developing comprehensive treatments that address both the nociceptive and affective dimensions of PDN.

Future therapeutic directions must focus on bridging the gap between preclinical findings and clinical applications. Key priorities include: (1) Mechanistic exploration: elucidating the specific roles of DRG neuronal subpopulations and their interactions with non-neuronal cells. (2) Advancing targeted therapies: leveraging nanotechnology, gene editing, and bioinformatics to refine drug delivery and develop precision medicine approaches. (3) Enhancing translational research: conducting robust clinical trials to validate preclinical discoveries and assess the long-term efficacy and safety of novel interventions. Additionally, non-pharmacological approaches such as DRG stimulation, photobiomodulation therapy (PBMT), and electroacupuncture (EA) have shown promise in preclinical and early clinical studies [164-166]. These strategies may complement pharmacological treatments, offering a multimodal approach to PDN management.

In summary, the pathophysiology of PDN spans a continuum from peripheral to central systems. By combining molecular and systems-level approaches, future research can unravel the intricate network underlying PDN, ultimately leading to innovative treatments that improve patient outcomes and quality of life.

### Author Contributions

The authors contributed equally to all aspects of the article.

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### Conflict of interests

The authors declare no competing financial interests. ♦

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