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REVIEW ARTICLE

The role of protein kinases in diabetic neuropathic pain: an update review

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Abstract

Objectives Diabetic neuropathic pain (DNP) is a debilitating symptom of diabetic neuropathy which seriously impairs patient's quality of life. Currently, there is no specific therapy for DNP except for duloxetine and gabapentin that show limited utility in alleviating DNP. The present review aims to discuss the central role of protein kinases in the pathogenesis of DNP and their therapeutic modulation.

Methods Scopus, PubMed, and Google scholar were searched up to January 2022 to find relevant studies with English language in which the roles of proteins kinases in DNP were examined.

Results DNP is associated with hyperactivity in pain sensory neurons and therapies aim to specifically suppress redundant discharges in these neurons without affecting the activity of other sensory and motor neurons. Transient receptor potential vanilloid 1 (TRPV1) and purinergic 2×7 receptors ($P2\times7R$) are two receptor channels, highly expressed in pain sensory neurons and their blockade produces remarkable analgesic effects in DNP. The activities of receptor channels are mainly regulated by the protein kinases whose modulation provides remarkable analgesic effects in DNP models.

Conclusion Capsaicin, TRPV1 modulator, is the only agent successfully examined in clinical trials with promising effects in patients with DNP. Current data suggest that blocking calcium calmodulin dependent protein kinase II (CaMKII) is superior to other approaches, considering its pivotal role in regulating the pain neuron potentials. By this means, DNP alleviation is achievable without affecting the activity of other sensory or motor neurons.

Keywords Diabetic neuropathy · Diabetic neuropathic pain · Protein kinase

Introduction

Diabetes is the largest global epidemic of the current century, affecting 425 million people worldwide, and diabetic neuropathy is one of its common complications that occurs in nearly half of all diabetic patients. Diabetic neuropathy is caused by damage to the peripheral (both motor and sensory) and autonomic neurons [1], and the most common form of diabetic neuropathy is distal symmetric polyneuropathy where the extremities (hands, toes, and feet) are commonly affected. It manifests as motor weakness and sensory symptoms including paresthesia (abnormal painless sensations like numbness, tingling, itching), dysesthesia (abnormal painful sensations like pricking, burning, ice-old), allodynia (pain evoked by normally nonpainful stimuli like touching, running of water), and hyperalgesia (exaggerated pain sensation in response to mild painful stimuli) [2, 3]. Diabetic neuropathic pain (DNP) is a general term

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that encompasses dysesthesia, allodynia, and hyperalgesia which markedly impairs patients' life quality, affects sleep, work, self-esteem, and social relations, and results in social abstentions and depression [4]. Generally, one quarter of all diabetic patients suffer from DNP [5].

In DNP, a physical damage to pain neurons is not the major problem, rather pain sensory neurons become hyperactive and discharge frequently in this condition. Pain sense is transmitted to the central nervous system by dorsal root ganglia (DRG) and through un-myelinated C- and thinly myelinated A-fibers, and it is now known that the sensitization and hyperactivity of these neurons are the mainstay of DNP [6]. In the last two decades, efforts have been made to elucidate the molecular basis underlying the neuronal hyperactivity in DNP in order to tailor specific and effective treatment methods for the condition [7]. A-fiber neurons in the DRG are large-diameter neurons with thinly myelinated axons that convey the pain sensation, and have pivotal roles in the induction of allodynia in neuropathic pains [8].

A protein kinase is a kinase enzyme that enacts protein phosphorylation by covalently adding a phosphate group from adenosine triphosphate (ATP) to an amino acid residue in a protein. Protein phosphorylation is a reversible post-translational modification which alters the protein conformation, and results in either target activation or deactivation. Protein kinases are categorized into two main types: 1- serine/threonine kinases, that target the hydroxyl groups of serine or threonine residues in the downstream proteins, and 2- tyrosine kinases, which phosphorylate the tyrosine residues in their targets [9]. Kinases are extremely crucial for cell biology as ~30% of all human proteins could be modified by kinases; and therefore, these enzymes regulate the majority of cellular functions [10].

Molecular pathogenesis of DNP: the central role of receptor channels

Receptor channels, also called ligand-gated ion channels, are a set of transmembrane multimeric proteins located on the neurons, that open to allow the passage of diverse ions like Na^+, K^+, Ca^{2+}, and/or Cl^- in response to the binding of a chemical messenger (i.e. a ligand), such as a neurotransmitter [11]. These channels act to regulate or control the function of neurons, and depending on the ion that allow in or out of the cell, they stimulate or suppress the neuronal function. For instance, increased load of Cl^- ions inside neurons opposes the induction of action potential, making the neurons less excitable; conversely, increased load of positively charged ions such as Na^+ and Ca^+ decreases the stimulatory threshold and renders the neurons hyperactive [12, 13]. Under diabetic conditions, the expression of receptor channels as well as the production of neurotransmitters are altered which affects the activity of neurons. Therefore, recognizing the pathophysiology of receptor channels in diabetes will elucidate the nature of neuronal derangements seen in these patients and helps in tailoring more targeted therapies [14].

The transient receptor potential vanilloid 1 (TRPV1) is a ligand-gated nonselective cation channel that specifically localizes to C- and A-fiber (nociceptive) sensory neurons [15]. TRPV1 activation allows for the inflow of Na^+ and Ca^{2+} ions, initiating nerve depolarization. This key role of TRPV1 in nociception has been corroborated by the finding that TRPV1-knockout mice had decreased pain response following thermal hyperalgesia [16]. Kamei et al., were the first scholars to show that intrathecal injection of anti-TRPV1 serum to diabetic mice alleviated thermal allodynia [17]. Moreover, substance P is the main neurotransmitter in afferent pain fibers, whose expression is greatly increased in neuropathic pains, and it has been evidenced that capsaicin, a TRPV1 activator, triggers these neurons to eventually deplete their substance P reserves, causing pain attenuation both in diabetic mice and in human patients; in fact, prolonged exposure to capsaicin desensitizes the pain nociceptors [18]. Capsaicin 8% patch causes no neurologic adverse effects in diabetic patients [19] and attenuates pain two weeks after the treatment onset [20]. Similarly, capsazepine, a TRPV1 antagonist, effectively alleviated pain in rat, mouse, and guinea pig models of capsaicin-induced, inflammatory, and neuropathic pains [21].

The transient receptor potential M8 (TRPM8), formerly called menthol and cold receptor 1 (CMR1), is the other non-selective ion channel present on pain sensory neurons. Its role in neuropathic pains is less investigated compared to TRPV1. TRPM8 contributes to cold sensation and is evoked by temperatures lower than 25°C, as well as by cooling agents like menthol and icilin [22]. TRPM8 activation results in the influx of Na^+ and Ca^{2+} with the consequent membrane depolarization [23]. phosphatidylinositol 4,5-bisphosphate (PIP_2) is the pivotal regulator of TRPM8 channels, as exogenous PIP_2 activates them in DRG neurons in vitro; conversely, inhibition of phosphoinositide (PI) 4-kinase, the enzyme responsible for PIP_2 synthesis, by either wortmannin or phenylarsine oxide (PAO) downregulated the TRPM8 activity [24]. Total protein levels as well as phosphorylated forms and the activity of TRPM8 channels are increased in the DRG neurons of diabetic mice, and both protein kinase A and protein kinase C contribute significantly to the enhanced activities of these channels. Moreover. Specific inhibition of TRPM8 channels significantly attenuates pain indices in diabetic mice [25].

Acid sensing ion channel 1 (ASIC1) is a proton-gated cation channel which allows for the influx of Na^+ ions, and

is widely expressed in nociceptive neurons [26]. It has been shown that ASIC1 protein levels are increased in the DRG neurons of diabetic rats [27]. However, it is not yet known that whether the activity of ASIC1 is altered under diabetic circumstances or not, and if ASIC1 stimulation or blockade has any therapeutic utility in DNP. Therefore, more thorough investigations are needed to answer these questions.

Orphan G protein–coupled receptor 177 (GPR177) is a seven-transmembrane protein and is principally expressed in A-fiber DRG neurons that regulates the secretion of wingless-type mammary tumor virus integration (Wnt) ligands [28]. Despite not being an ion channel, it is discussed here because GRP177 is closely related to TRPV1 function. GRP177 is specifically up-regulated in A-fiber DRG neurons and exclusively secretes Wnt5a from these neurons in diabetic mice. Wnt5a secretions is essential for allodynia and hyperalgesia as its blockade abrogates these symptoms in diabetic mice. Wnt5a increases intracellular levels of Ca^{2+} and in turn activates the TRPV1 channels [29].

Purinergic 2 × 7 receptors (P2 × 7R) are non-selective cation channels that are principally expressed in the DRG neurons. These receptor channels are mainly activated by the extracellular adenosine triphosphate (ATP). In neuropathic conditions, the ATP released from the injured neurons and glial cells stimulate P2 × 7Rs on the intact pain neurons [30]. P2 × 7R is also present on the glial cells of DRG whose stimulation leads to the release of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and plasminogen which aggravate the neuropathic pain [31]. It was detected in diabetic rats that the expression of P2 × 7R in DRG neurons is increased, and intrathecal administration of A438079, the P2 × 7R antagonist, improved allodynia and pain indices, and simultaneously decreased protein levels of TRPV1. Moreover, it decreased IL-1β levels (a pro-inflammatory cytokine) and elevated IL-10 levels (an anti-inflammatory cytokine). It was found that P2 × 7R inhibition reduced the expression of TRPV1 by down-regulating the MAPK signaling pathway [32]. Another study conducted on diabetic rats reported that either silencing P2 × 7R or inhibiting p38 improved allodynia, attenuated both TRPV1 and PKC expressions, and simultaneously decreased IL-1β levels by suppressing NF-kB activity [33].

Cannabinoid 2 receptor (CB2R) is expressed on the DRG neurons whose activation produces analgesia. Intrathecal administration of AM1241 and AM1710, the CB2R agonists, in rats with sciatic nerve injury alleviated allodynia and suppressed inflammation in the dorsal horn of the spinal cord [34]. It should be underlined that the increased levels of neuroimmune chemokine, C–C class chemokine-2 (CCL2), also called monocyte chemo-attractant protein-1 (MCP-1), in the dorsal horn of spinal cord increases the expression of TRPV1 on DRG neurons [35]. However, it has been shown that AM1710 (CB2R agonist) attenuates allodynia both independently of TRPV1 and by down-regulating TRPV1 expression on DRG neurons [36].

Protein kinase C (PKC)

PKC is a serine/threonine kinase which controls the function of other proteins by phosphorylation. PKC is mainly activated by diacylglycerol (DAG), a second messenger lipid, which is generated by hydrolysis from the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) by the function of membrane-anchored enzyme phospholipase C (PLC). Inositol trisphosphate (IP_3) is the other product of PLC which enters the cytosol and induces the release of calcium ions from the smooth endoplasmic reticulum, whereas DAG does not diffuse in to the cytoplasm, remains in the plasma membrane due to its hydrophobic properties and directly activates PKC. Moreover, PKC can be activated by calcium ions (Ca^{2+}) [37].

PKC is expressed in high concentrations in neuronal tissues and is involved in a wide array of neuronal functions [38]. PKC activates TRPV1 by phosphorylation. It has been demonstrated that TRPV1 could solely be activated by PKC, even in the absence of TRPV1 agonist. TRPV1 activation was augmented by tetradecanoylphorbol acetate (TPA), a PKC activator; and its activity was reduced by bisindolylmaleimide (BIM), a PKC inhibitor [39]. These findings were confirmed in vivo by two independent studies, as it was shown that both phosphorylated protein levels and the activity of DRG neurons were increased in rats with diabetes; and these effects were enhanced after administering a PKC activator, and were abrogated after injecting a PKC inhibitor [40, 41].

Advanced glycation end products (AGEs) are formed in excess quantities in diabetes by non-enzymatic reaction of glucose with proteins. AGEs contribute to the pathogenesis of diabetic complications by activating the receptor for advanced glycation end products (RAGEs), expressed on various cell types [42]. High glucose concentrations evoke the TRPV1 activity in mice DRG neurons in vitro while the cell viability was not affected in the high glucose medium. Interestingly, RAGE-knockout DRG neuros demonstrated no hyperactivity in high glucose medium; likewise, wild-type DRG neurons exposed to antioxidants α-lipoic acid plus catalase showed no hyperactivity in the same medium. Finally, inhibition of either PKC or Drc kinase abrogated RAGE-mediated hyperactivity in DRG neurons, suggesting that RAGE contributes to the hyperactivity of TRPV1 channels by activating PKC and Src kinase [43].

Protein kinase (PKA)

PKA, also called cAMP-dependent protein kinase, is a kinase which is regulated by cyclic AMP (cAMP). Extracellular molecules such as serotonin, prostaglandins, and epinephrine modulate nociception by first binding to a G protein–coupled receptor (GPCR) on the neuron. When activated, a conformational change is induced in the receptor that is transmitted to an attached intracellular heterotrimeric G protein complex through protein domain dynamics. The Gs alpha subunit of the stimulated G protein complex exchanges GDP for GTP in a reaction catalyzed by the GPCR and is released from the complex. The activated Gs alpha subunit binds to and activates an enzyme called adenylyl cyclase, which, in turn, catalyzes the conversion of ATP into cAMP, directly increasing the cAMP level.

It has been shown that the injection of membrane permeable cAMP or adenylyl cyclase activators lower the nociceptive threshold and lead to hyperalgesia in experimental models [44]. Mechanistically, PKA phosphorylates the hyperpolarization activated cation channels (HCN) on the nociceptive neurons to allow in more positively charged ions, leading to frequent nerve activation [45]. PKA also induces the activity of voltage-gated sodium channels on the pain sensory nerves which augments their excitability [46]. It has been shown that dexmedetomidine relieves hyperalgesia induced by brachial plexus root avulsion by suppressing PKA [47]. PKA is also able to directly phosphorylate TRPV1 channels. It has been shown that prostaglandin E2 (PGE2) induces hyperalgesia by increasing intracellular c-AMP levels (PKA activation); conversely, the μ-opioid agonists produce analgesic effects by decreasing intracellular c-AMP levels (PKA inhibition) [48].

Protein kinase B (PKB)

PKB, also commonly called Akt, is another serine/threonine protein kinase that has multiple roles in various cellular functions including cell survival, proliferation, and apoptosis [49]. unlike other protein kinases, PKB is part of the PI3K/Akt/mTOR signaling pathway; and it is activated by phosphoinositide 3-kinase (PI3K), and then activates the downstream kinase, mammalian target of rapamycin (mTOR) which is the main effector protein kinase of this pathway [50]. mTOR activation downregulates autophagy in neuronal tissues, limiting the cells adaptive properties and contributes to the pathogenesis of neuropathic pains [51]. Impaired autophagy is associated with increased activity of pain sensory fibers in rats, exacerbating allodynia and hyperalgesia indices [52]. It has been shown that in the DRG neurons of diabetic rats, the phosphorylated levels of all PI3K, PKB, and mTOR are increased, suggesting the activation of this pathway; and the levels of belcin-1 and LC3-II, the autophagy-related proteins, are decreased, suggesting the inhibition of autophagy. It was found that LY294002, the PI3K inhibitor, reversed the above-mentioned indices and significantly attenuated pain perception in diabetic rats [53]. Whether PI3K/Akt/mTOR activation in the pain sensory neurons of diabetic rats affects TRPV1 channels or not has not been investigated yet.

Calcium/calmodulin-dependent protein kinase (CaMK)

CaMK is a serine/threonine kinase activated by elevations in the intracellular levels of Ca^{2+} and calmodulin. As a calcium-binding protein, calmodulin is being targeted by the secondary messenger Ca^{2+}. Ca^{2+}/calmodulin complex functions as part of a calcium signal transduction pathway by activating CaMK. Activated CAMK phosphorylates a broad spectrum of membrane-bound to transcription factor proteins, and thereby, regulates many cellular functions including cell division, proliferation, and programmed cell death [54]. CaMKII is the main isoform present in neuronal cells [55], and therefore, in the following lines the role of CaMKII will be discussed in DNP. In basal state, CaMKII is phosphorylated at Thr305. When Ca^{2+} binds CaMKII, it gains an auto-phosphorylating property to be self-phosphorylated on Thr286 which is the active form of the enzyme [56]. Auto-phosphorylated CaMKII does not need further stimulation by calcium and it can maintain its activity independent of further stimuli, providing a function of molecular memory [57].

Nearly a decade ago, two independent experimental studies on rat models of diabetes demonstrated increased protein expression and phosphorylation of CaMKII in DRG neurons. According to these reports, the α isoform of CaMKII was the predominant form, and that the increased CaMKIIα activity was associated with pain-related behavior in rats [58, 59]. Increased activity of CaMKIIα in trigeminal nerves of diabetic rats has been noticed [60]. Moreover, myristoylated autocamtide-2-inhibitory peptide (AIP) produces analgesia in rats with sciatic nerve mononeuropathy by inhibiting the CaMKII [61]. Both total protein and phosphorylated forms of CaMKII are increased in the DRG neurons of diabetic rats, and KN-93, the CaMKII inhibitor, alleviates hyperalgesia, in addition to reducing phosphorylated CaMKII and P2 × 3R levels [62].

N-methyl-D-aspartate receptor (NMDAR) is a receptor-channel activated by the salient excitatory neurotransmitter glutamate, and is widely expressed on pain sensory neurons [63]. Upon activation, it allows for the inflow of Ca^{2+} ions.

It was first demonstrated by Matsumura and colleagues that NMDAR-knockout mice had decreased allodynia in sciatic neuropathic pain. Moreover, in NMDAR-knockdown mice, the concentration of intracellular Ca^{2+} did not increase as much as the wild-type mice. Indeed, pT286-CaMKII levels did not increase in NMDAR-knockdown mice, whereas, its levels were significantly elevated in wild-type mice [64]. These findings suggested that CaMKII has a key role in nociception in neuropathic pains. (Fig. 1)

Capsaicin cannot be administered orally due to its gastrointestinal side effects. Fajrin et al., investigated 6-shogoad, a chemical agent extracted from ginger with structural similarity to capsaicin, in diabetic rats and found that this agent alleviated thermal allodynia and suppressed the gene expressions of both TRPV1 and NMDAR in the DRG neurons of rats. Interestingly, 6-shogoal treatment intensified insulin immunoreactivity in the pancreatic islets cells of diabetic rats, a unique feature that has not been reported for capsaicin [65].

The central role of NMDAR in pain perception has been shown in rats with induced trigeminal nerve pain as inducing NMDAR enhanced pain perception and inhibition of NMDAR resulted in reduced pain feeling. NMDA acted by stimulating TRPV1 activity as blocking TRPV1 channels abrogated NMDA-evoked pain. Moreover, it was found that NMDA increased the activities of both PKC and CaMKII, and these proteins phosphorylated TRPV1 channels. Interestingly, PKA inhibition resulted in reduced pain perception, however, its mechanism of action was independent from TRPV1 because chemical activation of PKA did not increase phosphorylated TRPV1 levels [66].

Modulating TRPV1 activity also impacts CaMKII, as it has been demonstrated in a rat model of neuropathic pain that silencing TRPV1 suppresses the expression of CaMKII and declines phosphorylated ERK levels in DRG neurons [67]. In addition to CaMKII, the role of CaMKIV in neuropathic pain has also been investigated. Zhao and colleagues reported that CaMKIV inhibition reduced HMGB1 expressions in DRN neurons of diabetic rats, alleviating the thermal hyperalgesia and mechanical allodynia. Therefore, dual blockade of CaMKII and CaMKIV can produce more efficient analgesic effects [68].

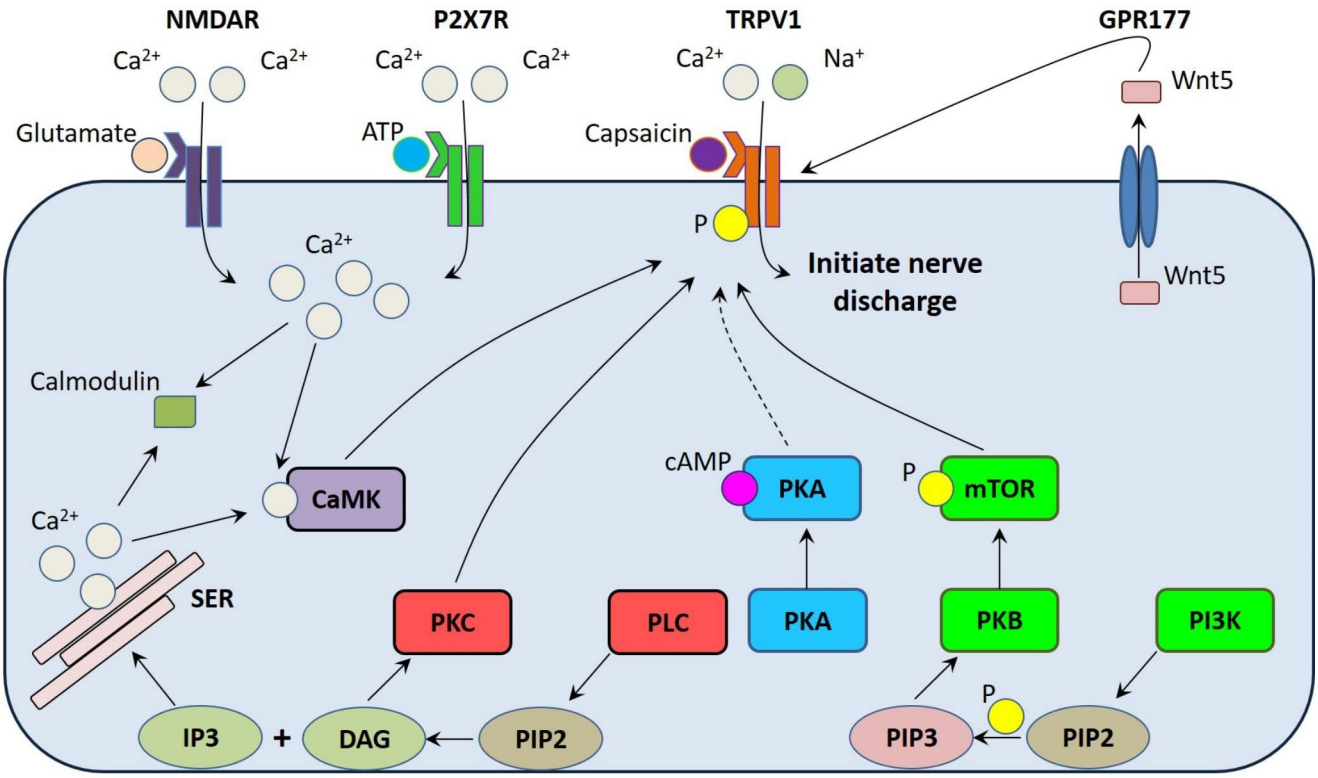

Fig. 1 Overview of the role of receptor channels and protein kinases in pain sensory neuron hyperactivity. ATP, adenosine triphosphate; CaMK, calcium/calmodulin dependent protein kinase; cAMP, cyclic adenosine monophosphate; DAG. diacylglycerol; IP3, inositol trisphosphate; GPR177, orphan G protein–coupled receptor 177; mTOR, mammalian target of rapamycin; NMDAR, N-methyl-D-aspartate receptor; P, phosphate; P2 × 7R, purinergic 2 × 7 receptor; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol triphosphate; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PLC, phospholipase C; SER, smooth endoplasmic reticulum; TRPV1, Transient receptor potential vanilloid 1

Conclusion

Diabetic neuropathic pain is an important sequela of diabetic neuropathy which deeply affects patient's life quality. It is related to abnormally increased activity of pain sensory neurons and therefore neither steroidal nor non-steroidal anti-inflammatory drugs are effective in alleviating DNP. Therapeutic goal is to specifically suppress pain sensory neurons, without affecting motor as well as other sensory neurons. Opioid analgesics are not routinely prescribed for DNP due to their broad spectrum of side effects. Currently, DNP is mainly managed by duloxetine or venlafaxine (serotonin–norepinephrine reuptake inhibitor antidepressants) and pregabalin, or gabapentin (gabapentinoid anticonvulsants). Again, these agents are non-specific and are switched if there is no response or if side effects develop. TRPV1, P2 × 7R, and NMDAR are receptor channels mainly expressed on pain sensory neurons and their modulation attenuates diabetes associated pain with no effect on other nervous functions; for instance, the safety and efficacy of %8 capsaicin dermal patch has been proved in large scale clinical studies. However, the majority of studies are at the experimental levels and conducting clinical trials to evaluate the safety and efficacy of these therapeutic modalities are highly warranted.

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Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

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