Original Article

GLP-1 Receptor Signaling Partially Mediates Sitagliptin-Induced Neuroprotection in Experimental Neuropathic Pain Following Chronic Constriction Injury

Somayeh Delfani[1], Farzaneh Bagheri[2], Ali Rashidian-Rashidabadi[3], Sanaz Mokhtari[4], Samad Darabian[5], Abolfazl Abbaszadeh[6*]

[1] Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran.

[2] Department of Physiology and Pharmacology "V. Erspamer" University Sapienza of Rome, Rome, Italy.

[3] Department of Anatomical Science, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran.

[4] Department of Pharmacotherapy, School of Pharmacy. Mazandaran University of Medical Sciences, Sari, Iran.

[5] Department of Statistics and Epidemiology, Faculty of Health, Isfahan University of Medical Sciences, Isfahan, Iran.

[6] Department of Plastic and Reconstructive Surgery, Hazrat Fatemeh Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

***Corresponding author:** Abolfazl Abbaszadeh, Department of Plastic and Reconstructive Surgery, Hazrat Fatemeh Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
E-mail: dr.abol.abbaszadeh@gmail.com

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Abstract:

Background: Peripheral nerve injury frequently leads to persistent neuropathic pain accompanied by sensory and motor dysfunction. The chronic constriction injury (CCI) model reproduces key pathological features of peripheral neuropathy, providing a well-established experimental platform for evaluating neuroprotective therapies. This study investigated the neuroprotective effects of sitagliptin and examined the contribution of glucagon-like peptide-1 receptor (GLP-1R) signaling to its therapeutic effects in CCI-induced neuropathic pain.

Materials and Methods: Twenty-eight adult male Wistar rats were randomly allocated into four groups: Sham, CCI, CCI + Sitagliptin, and CCI + Sitagliptin + Exendin (9–39), a GLP-1R antagonist. Pain-related behaviors, motor nerve conduction velocity (MNCV), inflammatory biomarkers (IL-1β and CRP), and sciatic nerve histopathology were evaluated.

Results: CCI induced marked pain hypersensitivity, reduced MNCV, increased inflammatory biomarker levels, and severe sciatic nerve injury. Sitagliptin significantly alleviated pain-related behaviors, improved MNCV, reduced IL-1β and CRP levels, and preserved nerve architecture. Co-administration of Exendin (9–39) partially attenuated these protective effects, supporting the involvement of GLP-1R signaling while suggesting the contribution of additional GLP-1-independent mechanisms.

Conclusion: Sitagliptin exerts neuroprotective and anti-inflammatory effects in experimental neuropathic pain, with GLP-1R signaling contributing to these protective actions. These findings support the therapeutic potential of sitagliptin as a promising pharmacological strategy for the management of neuropathic pain.

Mechanistic and Translational Relevance: Sitagliptin-mediated neuroprotection in CCI-induced neuropathic pain involves partial contribution of GLP-1 receptor signaling, as pharmacological GLP-1R blockade attenuated its beneficial effects on pain behaviors, nerve conduction, inflammatory responses, and nerve morphology. The incomplete reversal by Exendin (9–39) suggests the involvement of additional GLP-1R-independent mechanisms. These findings highlight the potential repurposing of sitagliptin as a neuroprotective strategy beyond its established metabolic indications and provide a rationale for further investigation in peripheral neuropathic conditions.

Keywords: Sitagliptin; Dipeptidyl Peptidase-4 Inhibitor; GLP-1 Receptor Signaling; Neuropathic Pain; Peripheral Nerve Injury; Neuroinflammation

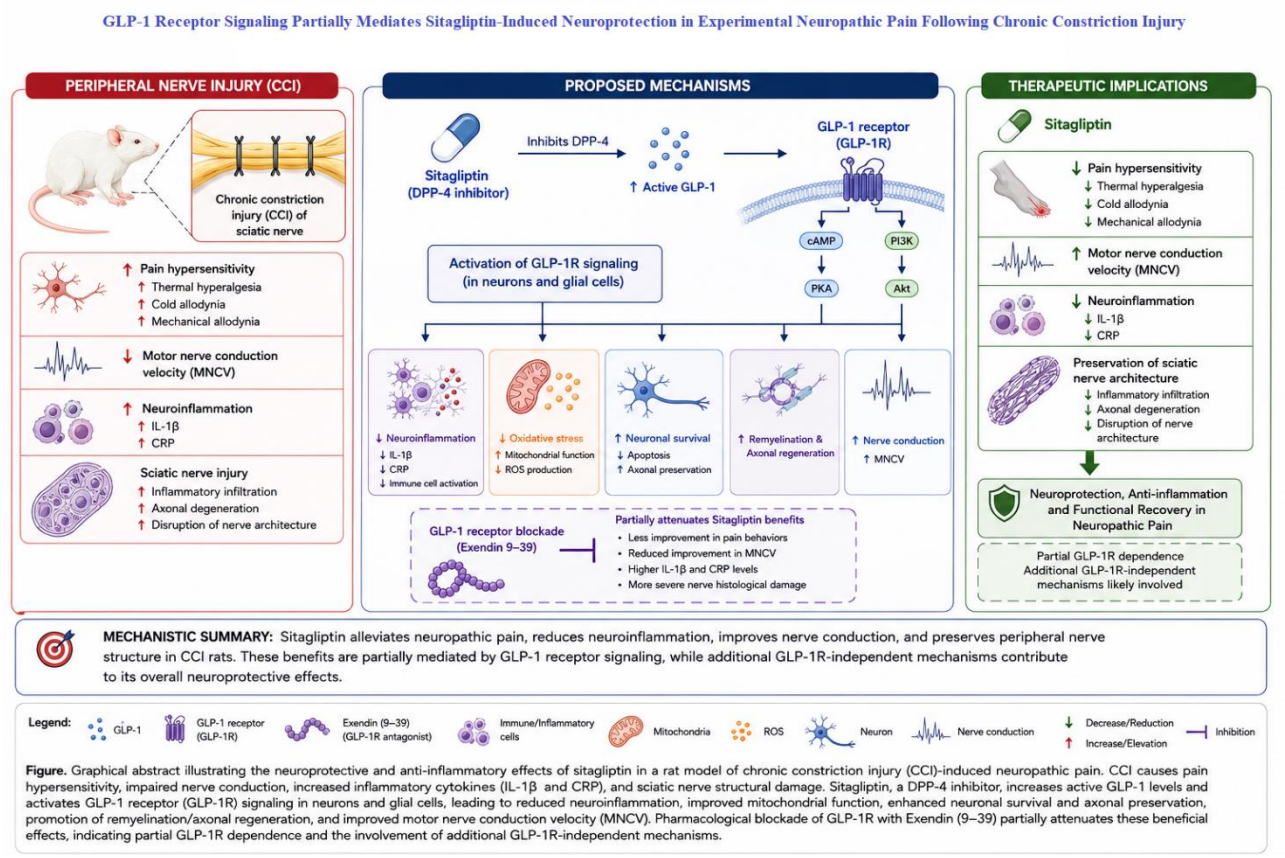

Figure. Graphical abstract illustrating the neuroprotective and anti-inflammatory effects of sitagliptin in a rat model of chronic constriction injury (CCI)-induced neuropathic pain. CCI causes pain hypersensitivity, impaired nerve conduction, increased inflammatory cytokines (IL-1β and CRP), and sciatic nerve structural damage. Sitagliptin, a DPP-4 inhibitor, increases active GLP-1 levels and activates GLP-1 receptor (GLP-1R) signaling in neurons and glial cells, leading to reduced neuroinflammation, improved mitochondrial function, enhanced neuronal survival and axonal preservation, promotion of remyelination/axonal regeneration, and improved motor nerve conduction velocity (MNCV). Pharmacological blockade of GLP-1R with Exendin (9–39) partially attenuates these beneficial effects, indicating partial GLP-1R dependence and the involvement of additional GLP-1R-independent mechanisms.

Graphical Abstract: Mechanistic and Translational Overview of Sitagliptin-Mediated Neuroprotection Through GLP-1 Receptor Signaling Following Chronic Constriction Injury. Peripheral nerve injury induces neuroinflammation, pain hypersensitivity, impaired motor nerve conduction, and structural damage to the sciatic nerve. As a dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin increases endogenous GLP-1 availability and activates GLP-1R signaling in neurons and glial cells, leading to suppression of inflammatory responses, preservation of neuronal integrity, promotion of axonal regeneration and remyelination, improvement of motor nerve conduction velocity (MNCV), and attenuation of thermal hyperalgesia, mechanical allodynia, and cold allodynia. Pharmacological blockade of GLP-1R with Exendin (9–39) partially reverses these beneficial effects, resulting in increased inflammatory cytokine production (IL-1β and CRP), greater nerve injury, and diminished functional recovery. The incomplete reversal of sitagliptin-mediated protection suggests that additional GLP-1R-independent mechanisms also contribute to its overall neuroprotective actions, supporting the therapeutic potential of sitagliptin for the treatment of peripheral neuropathic pain.

Introduction

Peripheral nerve injury is a prevalent clinical problem that frequently results in sensory deficits, motor dysfunction, and persistent neuropathic pain (1). These injuries trigger substantial structural and functional alterations in axons and myelin, ultimately impairing nerve signal transmission (2). Concurrently, activation of inflammatory pathways and release of pain-associated mediators disrupt normal regenerative processes in peripheral nerves, contributing to the chronicity of symptoms (3). The transition from acute nerve injury to chronic neuropathic pain is largely mediated by neuroinflammatory mechanisms, which sustain abnormal nociceptive signaling over time (4). The interaction between activated glial cells and immune elements amplifies neuroinflammatory signaling through the upregulation of pro-inflammatory cytokines, particularly TNF-α, IL-1β, and IL-6. Elevated levels of these cytokines facilitate peripheral and central sensitization while contributing to neuronal degeneration (5). These

inflammatory mediators not only impair nerve regeneration but also contribute to central sensitization and persistent pain states (6). Understanding the cellular and molecular mechanisms underlying peripheral neuropathy is therefore critical for the development of effective therapeutic strategies (7). Studies using this model have demonstrated that neuroinflammation, neuronal dysfunction, and structural nerve injury are key contributors to CCI-induced neuropathic pain, identifying several potential therapeutic targets (8). Among these pathways, the DPP-4/GLP-1 signaling axis has recently emerged as a key regulator of neuronal function and neuroprotection (9). The glucagon-like peptide-1 receptor (GLP-1R) is expressed in both neurons and glial cells, where its activation suppresses neuroinflammation by reducing the production of pro-inflammatory cytokines, promotes neuronal survival, and facilitates nerve repair following peripheral nerve injury (10, 11). Additionally, GLP-1R signaling modulates nitric oxide (NO) homeostasis by reducing inducible nitric oxide synthase (iNOS) activity while preserving endothelial nitric oxide synthase (eNOS) function (12, 13). These neuroprotective mechanisms position GLP-1R as a promising therapeutic target in peripheral nerve injury.

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor widely used in diabetes management, elevates circulating levels of active GLP-1 (14). Beyond its glucose-lowering effects, sitagliptin has demonstrated anti-inflammatory and neuroprotective properties across multiple experimental models (15, 16). Emerging evidence suggests that sitagliptin exerts anti-inflammatory and neuroprotective effects while improving functional recovery, at least in part through GLP-1R-dependent mechanisms (17). However, whether the neuroprotective effects of sitagliptin in CCI-induced neuropathic pain are predominantly mediated through GLP-1R signaling or involve additional GLP-1-independent mechanisms remains unclear. In particular, it is not well established whether the beneficial effects of sitagliptin are entirely dependent on GLP-1R activation or involve additional mechanisms. Therefore, the present study was designed to determine the contribution of GLP-1R signaling to the neuroprotective effects of sitagliptin in a rat model of CCI-induced neuropathic pain using pharmacological GLP-1R blockade with Exendin (9–39).

Methods

In this study, twenty-eight adult male Wistar rats (230–250 g) were obtained from the institutional animal facility. The study protocol was approved by the Ethics Committee of Lorestan University of Medical Sciences (Approval No. IR.LUMS.REC.1395.184). All experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Lorestan University of Medical Sciences and were conducted in strict accordance with the Guide for the Care and Use of Laboratory Animals issued by the Ministry of Health. Throughout the study, animals were provided with ad libitum access to food and water and were maintained under a controlled 12-hour light/12-hour dark cycle. Bedding was regularly replaced to ensure hygiene and animal welfare. Following a three-day acclimation period, animals were randomly assigned to four experimental groups (n = 7 per group) to evaluate the effects of sitagliptin and Exendin (9–39) in the CCI model. Randomization was performed using a computer-generated random allocation sequence to minimize selection bias. The sample size was determined by an a priori power analysis using G*Power software (version 3.1). Assuming an effect size (f) of 0.70, a significance level (α) of 0.05, and a statistical power ($1 - \beta$) of 0.80, the minimum required sample size was

calculated to be seven animals per group. This sample size was considered sufficient to detect biologically relevant differences among the experimental groups while minimizing unnecessary animal use in accordance with the principles of the 3Rs (Replacement, Reduction, and Refinement).

Drug administration was performed by one investigator, whereas all behavioral assessments, electrophysiological measurements, histopathological evaluations, and data analyses were conducted independently by a second investigator who was blinded to the treatment allocation, thereby minimizing performance and detection bias. The experimental groups were defined as follows:

Group 1: Control (Sham) group – healthy animals with no CCI or drug treatment.

Group 2: CCI group – animals subjected to chronic constriction injury without treatment.

Group 3: CCI + Sitagliptin group – animals received Sitagliptin at 20 mg/kg via oral gavage.

Group 4: CCI + Sitagliptin + Exendin (9-39) group – animals received Sitagliptin (20 mg/kg, gavage) in combination with Exendin (9-39) (160 µg/kg, IP).

No animals were excluded from the study after randomization. All twenty-eight rats completed the experimental protocol and were included in the final behavioral, electrophysiological, biochemical, and histopathological analyses. Sitagliptin (Actoverco, Tehran, Iran) and Exendin (9-39) (BACHEM, Switzerland) were used in the study. The doses of Sitagliptin (18) and Exendin (9-39) (19) were selected based on previously published experimental studies. In all treatment groups, drug administration commenced one day prior to CCI induction and continued once daily for 15 consecutive days post-surgery. In the combination treatment group, Exendin (9–39) was administered intraperitoneally 30 minutes before oral sitagliptin administration to ensure effective GLP-1 receptor blockade prior to DPP-4 inhibition. Saline was used as the vehicle control for all compounds. Pain-related behavioral assessments were performed on days 3 and 15 following CCI. These time points were selected to represent the early inflammatory phase (day 3) and the established neuropathic phase (day 15) of CCI-induced neuropathic pain. Pentobarbital sodium (60 mg/kg, IP) was used exclusively for induction of the CCI surgery, whereas isoflurane anesthesia was used for subsequent electrophysiological assessments and tissue collection because it allows rapid induction and recovery while providing a stable anesthetic plane during these procedures. On day 15, immediately after behavioral testing, rats were anesthetized with isoflurane and positioned in the ventral recumbent posture. A small incision was made in the thigh muscle to expose the sciatic nerve for subsequent dissection and excision. All procedures were performed under aseptic conditions to minimize infection and variability. The excised nerve was then immersed in 10% neutral-buffered formalin for histopathological analysis.

Induction of Neuropathic Pain Using the CCI Model

Neuropathic pain was induced in rats using the CCI model of the sciatic nerve, according to the classical protocol described by Bennett and Xie (20, 21). Animals were prepared under sterile conditions. The thigh area was shaved, disinfected, and anesthesia (pentobarbital 60 mg/kg, IP) was administered to minimize pain and stress. A small incision was made in the mid-thigh, and the gluteal and biceps femoris muscles were carefully separated to expose the sciatic nerve. Four loosely tied ligatures were placed along the nerve at approximately 1-mm intervals using 4-0 chromic gut sutures (or equivalent). The ligatures were tight enough to induce mild nerve constriction without obstructing epineural blood flow, thus avoiding

complete ischemia. Muscles and skin were subsequently closed in layers.

Postoperatively, animals were housed individually and closely monitored to ensure proper recovery. All behavioral assessments were performed by investigators blinded to group assignments to minimize bias. In addition, data analysis was also performed under blinded coding conditions to further reduce potential assessment bias. Behavioral tests were conducted on days 3 and 15 post-CCI, and motor nerve conduction velocity (MNCV) was evaluated on day 15. These time points were selected to evaluate both early and late phases of neuropathic pain progression following nerve injury.

Behavioral Assessments

- Radiant Heat Plantar Test

Thermal hyperalgesia was assessed using the Radiant Heat Paw-Withdrawal Test (Hargreaves test) as previously described (22). Each rat was placed individually on a glass platform and allowed to acclimate for 15–20 minutes prior to testing. A radiant heat source was applied to the plantar surface of the hind paw, and paw withdrawal latency (PWL) was recorded in seconds as an index of pain sensitivity. This test specifically evaluates thermal hyperalgesia and is not related to mechanical sensitivity. Heat intensity was adjusted to elicit a withdrawal response within 10–15 seconds in control animals. Care was taken to avoid repeated stimulation of the same paw within a short interval and to minimize stress or tissue injury. All tests were conducted by investigators blinded to group assignments. In addition, data recording and extraction were performed under blinded coding conditions to reduce observer bias. Measurements were performed on days 3 and 15 following CCI. These time points were selected to assess both early and late phases of thermal hypersensitivity following peripheral nerve injury.

- Acetone Test

Cold allodynia was evaluated using the acetone test. A 100 µL drop of acetone was gently applied to the plantar surface of the hind paw. The animal's response was scored on a 0–3 scale: 0 = no response, 1 = brief flick or short withdrawal, 2 = repeated flicking or prolonged withdrawal, and 3 = repeated flicking accompanied by paw licking. Each rat received three applications at 5-minute intervals. During each session, responses were monitored for 60 seconds, with observations recorded every 20 seconds. All behavioral scoring was performed by an investigator blinded to group allocation to minimize observer bias. The cumulative score for each paw, ranging from 0 to 9, represented the overall intensity of cold allodynia. The scoring system was adapted from previously validated protocols to ensure reproducibility and comparability across neuropathic pain studies (23).

- Von Frey Test

Mechanical allodynia was assessed using a series of calibrated Von Frey filaments (2, 4, 6, 8, 10, 15, 26, and 60 g). Testing began with the filament exerting the lowest force, and if no paw withdrawal occurred, filaments with progressively higher forces were applied in ascending order. A positive response was defined as a clear and immediate paw withdrawal. When the animal exhibited two consecutive positive responses to the same filament, the corresponding force was recorded as the paw withdrawal threshold (PWT, g), and testing for that session was terminated. The paw withdrawal threshold (PWT) represents the minimum mechanical force required to evoke a nociceptive response and is used as an index of mechanical allodynia. If no response was observed even with the highest filament (60 g), a cutoff value of 60 g was assigned. Each assessment was repeated three times, with at least three minutes between trials to prevent sensitization. The mean of the three measurements was calculated as the final

PWT for each animal. All behavioral assessments were performed by an investigator blinded to group allocation to minimize observational bias (24).

- Evaluation of Motor Nerve Conduction Velocity (MNCV)

Motor nerve conduction velocity (MNCV) was measured non-invasively along the sciatic–posterior tibial nerve under temperature-controlled conditions. On day 15 post-CCI, rats were anesthetized with isoflurane, and core body temperature was maintained at 37 °C. The sciatic nerve was stimulated at two sites: proximally near the sciatic notch and distally just below the knee using bipolar electrodes connected to a NeuropackREMG system (Nihon Kohden, Japan). Muscle action potentials were recorded at the ankle using unipolar pin electrodes. Care was taken to ensure consistent electrode placement across all animals to minimize inter-animal variability. MNCV (m/s) was calculated by dividing the distance between the two stimulation sites by the difference in latency between proximal and distal stimulations. All measurements were performed by an investigator blinded to group allocation, and each recording was repeated to ensure signal stability before final analysis (25).

Measurement of Inflammatory Markers

On day 15, following behavioral testing and sciatic nerve excision, animals were anesthetized with isoflurane and euthanized in accordance with standard ethical guidelines. Rats were placed in a supine position, and the vertebral column was exposed from the cervical to lumbar regions. Surrounding tissues were carefully removed to enable complete excision of the spinal cord. To preserve tissue integrity, normal saline was infused from the cervical end to facilitate smooth extrusion of the cord through the lumbar region. The collected spinal cord tissues were immediately placed into sterile tubes, washed with ice-cold saline, and homogenized under cold conditions. Tissue processing was performed on ice to minimize protein degradation and preserve cytokine stability. After centrifugation, the supernatant was collected, and biochemical parameters, including IL-1β and CRP, were quantified using commercially available ELISA kits (Abcam, Abcam, Cambridge, UK) according to the manufacturers' protocols to ensure accuracy and reproducibility. Total protein concentrations were determined using the bicinchoninic acid (BCA) assay, and cytokine levels were normalized to the corresponding total protein content to minimize variability among samples. All samples were analyzed in duplicate to ensure assay reliability, and intra-assay variability was controlled according to kit specifications. Protein concentrations were normalized prior to analysis to account for inter-sample variability (26).

Histological and Morphological Analyses

The isolated sciatic nerve samples were fixed in 10% neutral-buffered formalin for 24–48 h and processed using standard histological procedures. Following routine dehydration, clearing, and paraffin embedding, tissue sections (5 µm thickness) were prepared using a microtome and stained with hematoxylin and eosin (H&E) according to standard protocols. All staining procedures were performed under identical conditions to minimize technical variability among samples. Histological evaluation was performed by an experienced pathologist blinded to the experimental groups. Sciatic nerve sections were examined using a light microscope for assessment of CCI-induced pathological alterations, including disruption of nerve fiber architecture, inflammatory cell infiltration, tissue degeneration, and perineural inflammatory changes. Representative photomicrographs were captured from each experimental group. Histopathological changes

were evaluated using a predefined semiquantitative scoring system based on the severity of morphological alterations. The scoring criteria were applied by the blinded pathologist to minimize observer bias and allow comparative analysis among experimental groups. The resulting histopathological scores were presented as quantitative data for statistical analysis (27).

- Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism software (version 8.0; GraphPad Software, San Diego, CA, USA). The normality of data distribution was assessed using the Shapiro–Wilk test, and homogeneity of variance was evaluated using Levene's test before applying parametric analyses. Behavioral data, including thermal hyperalgesia, cold allodynia, and mechanical allodynia, were analyzed using two-way repeated-measures ANOVA, with treatment as the between-subject factor and time (days 3 and 15) as the within-subject factor, followed by Bonferroni's multiple comparisons test. Biochemical parameters (IL-1β and CRP), motor nerve conduction velocity (MNCV), and histopathological injury scores were analyzed using one-way ANOVA followed by Bonferroni's multiple comparisons test. A two-tailed P value < 0.05 was considered statistically significant.

Result

Effects of Sitagliptin and GLP-1 Receptor Blockade on Thermal Hyperalgesia in the CCI Model

Evaluation of the radiant heat plantar test (Hargreaves test) demonstrated that on day 3 after CCI induction, animals in the CCI group exhibited a significant reduction in paw withdrawal latency (PWL) compared with the Sham group (P < 0.001), indicating increased thermal hypersensitivity. Sitagliptin treatment significantly increased PWL compared with the CCI group (P < 0.001), suggesting an early antinociceptive effect. Administration of Exendin (9–39) alone did not significantly alter PWL compared with the CCI group, and values remained significantly different from the Sham group (P < 0.001). On day 15 post-CCI, thermal hypersensitivity was further exacerbated in the CCI group, as evidenced by a greater reduction in PWL compared with Sham animals (P < 0.001). Sitagliptin significantly reversed this effect by increasing PWL relative to the CCI group (P < 0.001). Co-administration of Exendin (9–39) attenuated the analgesic effect of Sitagliptin, resulting in significantly lower PWL compared with Sitagliptin-treated animals (P < 0.001), although values did not fully return to CCI levels (Figure 1).

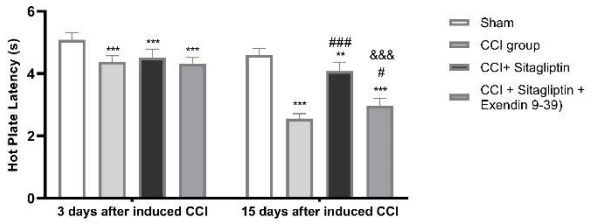

Figure 1. Assessment of Thermal Hyperalgesia in CCI Rats Following Sitagliptin and GLP-1 Receptor Blockade Treatment. Thermal hyperalgesia was assessed using the Hargreaves plantar test in rats subjected to chronic constriction injury (CCI) and treated with vehicle, sitagliptin (20 mg/kg, oral gavage), Exendin (9–39) (160 µg/kg, IP), or their combination for 15 consecutive days. Behavioral responses were evaluated on days 3 and 15 following CCI induction. Data are presented as mean ± SEM (n = 7 per group). *P < 0.05, **P < 0.01, ***P < 0.001 vs. Sham; #P < 0.05, ##P < 0.01, ###P < 0.001 vs. CCI; &P < 0.05, &&P < 0.01, &&&P < 0.001 vs. CCI + sitagliptin.

Impact of Sitagliptin and GLP-1 Receptor Blockade on Cold Allodynia in the CCI Model

Evaluation of cold allodynia using the acetone test showed no significant differences between the experimental groups on day 3 following CCI induction. On day 15, animals in the CCI group exhibited a significant increase in cold allodynia compared with the Sham group (P < 0.001), indicating enhanced sensory hypersensitivity.

Treatment with Sitagliptin significantly reduced cold allodynia scores compared with the CCI group ($P < 0.001$), demonstrating an analgesic effect. Inhibition of the GLP-1 receptor using Exendin (9–39) worsened cold allodynia, as evidenced by significantly higher scores compared with the Sitagliptin-treated group ($P < 0.01$) and the Sham group ($P < 0.001$). Co-administration of Exendin (9–39) with Sitagliptin significantly attenuated the analgesic effect of Sitagliptin, resulting in higher allodynia scores compared with Sitagliptin alone ($P < 0.01$) (Figure 2).

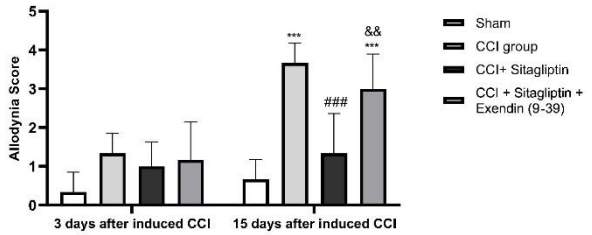

Figure 2. Assessment of Cold Allodynia in CCI Rats Following Sitagliptin and GLP-1 Receptor Blockade Treatment. Cold allodynia was assessed using the acetone drop test in rats subjected to chronic constriction injury (CCI) and treated with vehicle, sitagliptin (20 mg/kg, oral gavage), Exendin (9–39) (160 µg/kg, IP), or their combination for 15 consecutive days. Behavioral responses were evaluated on days 3 and 15 following CCI induction. Data are presented as mean ± SEM (n = 7 per group). *P < 0.05, **P < 0.01, ***P < 0.001 vs. Sham; #P < 0.05, ##P < 0.01, ###P < 0.001 vs. CCI; &P < 0.05, &&P < 0.01, &&&P < 0.001 vs. CCI + sitagliptin.

Effects of Sitagliptin and GLP-1 Receptor Blockade on Mechanical Allodynia in the CCI Model

Evaluation of mechanical allodynia using the Von Frey test showed no significant differences in paw withdrawal threshold (PWT) among the experimental groups on day 3 following CCI induction. On day 15 post-CCI, a significant reduction in PWT was observed in the CCI group compared with the Sham group ($P < 0.001$), indicating the development of mechanical allodynia. Treatment with Sitagliptin significantly increased PWT compared with the CCI group ($P < 0.001$), demonstrating an attenuation of mechanical hypersensitivity. Co-administration of Sitagliptin with Exendin (9–39) significantly reduced the analgesic effect of Sitagliptin, as evidenced by a lower PWT compared with the Sitagliptin-treated group ($P < 0.01$), and partially reduced PWT compared with the Sham group ($P < 0.05$) (Figure 3).

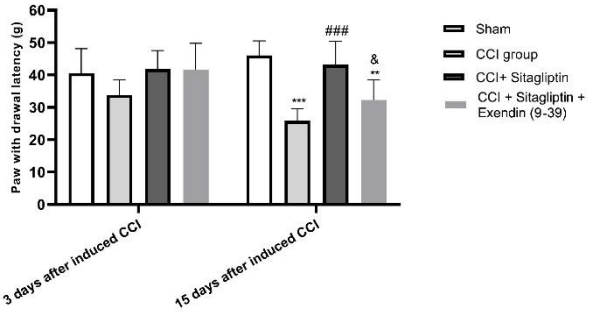

Figure 3. Assessment of Mechanical Allodynia in CCI Rats Following Sitagliptin and GLP-1 Receptor Blockade Treatment. Mechanical allodynia was assessed using the von Frey filament test in rats subjected to chronic constriction injury (CCI) and treated with vehicle, sitagliptin (20 mg/kg, oral gavage), Exendin (9–39) (160 µg/kg, IP), or their combination for 15 consecutive days. Behavioral responses were evaluated on days 3 and 15 following CCI induction. Data are presented as mean ± SEM (n = 7 per group). *P < 0.05, **P < 0.01, ***P < 0.001 vs. Sham; #P < 0.05, ##P < 0.01, ###P < 0.001 vs. CCI; &P < 0.05, &&P < 0.01, &&&P < 0.001 vs. CCI + sitagliptin.

Role of GLP-1 Receptor Signaling in MNCV Recovery in the CCI Model

Analysis of motor nerve conduction velocity (MNCV) revealed a significant reduction in sciatic nerve conduction following CCI induction compared to the Sham group ($P < 0.001$), indicating impaired nerve function. Treatment with Sitagliptin significantly improved MNCV compared to the CCI group ($P < 0.001$), suggesting a neuroprotective effect. In contrast, co-administration of Exendin (9–39) with Sitagliptin significantly reduced the improvement in MNCV compared with the Sitagliptin-only group ($P < 0.05$), implying that GLP-1 receptor signaling contributes to the neuroprotective effects of Sitagliptin (Figure 4).

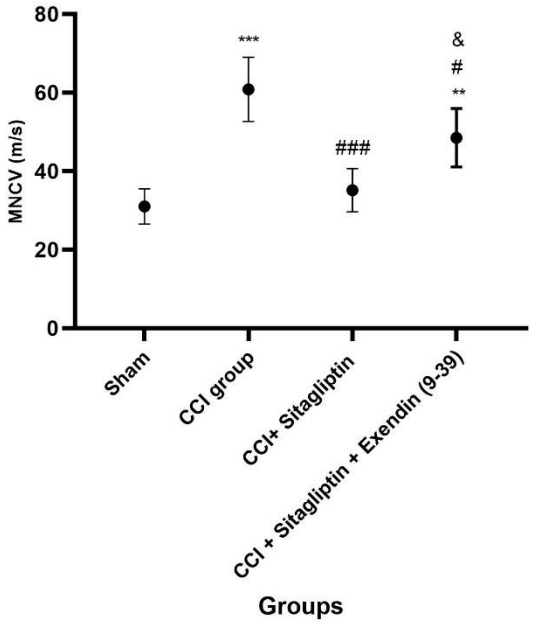

Figure 4. Assessment of Motor Nerve Conduction Velocity (MNCV) in CCI Rats Following Sitagliptin and GLP-1 Receptor Blockade Treatment. Motor nerve conduction velocity (MNCV) was assessed in rats subjected to chronic constriction injury (CCI) and treated with vehicle, sitagliptin (20 mg/kg, oral gavage), Exendin (9–39) (160 µg/kg, IP), or their combination for 15 consecutive days. MNCV was evaluated on day 15 following CCI induction. Data are presented as mean ± SEM (n = 7 per group). *P < 0.05, **P < 0.01, ***P < 0.001 vs. Sham; #P < 0.05, ##P < 0.01, ###P < 0.001 vs. CCI; &P < 0.05, &&P < 0.01, &&&P < 0.001 vs. CCI + sitagliptin.

Role of GLP-1 Receptor Signaling in Inflammatory Cytokine Regulation in the Spinal Cord in the CCI Model

Analysis of IL-1β levels (Figure 5) revealed that Sitagliptin administration significantly reduced IL-1β concentrations in the CCI group compared to the Sham group (P < 0.001), suggesting a potent anti-inflammatory effect. In contrast, inhibition of GLP-1 receptor signaling with Exendin (9–39) resulted in a significant increase in IL-1β levels compared to the Sitagliptin-treated group (P < 0.05), highlighting the role of GLP-1 receptor activation in modulating inflammatory responses. Similarly, analysis of CRP levels (Figure 6) demonstrated that Sitagliptin treatment significantly decreased CRP concentrations relative to the CCI group (P < 0.01). However, co-administration of Exendin (9–39) partially reversed this anti-inflammatory effect, with higher CRP levels observed compared to Sitagliptin treatment alone (P < 0.05).

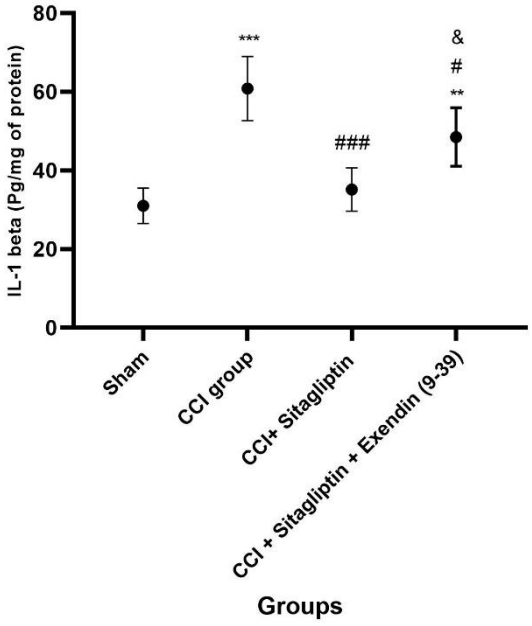

Figure 5. Assessment of Spinal Cord IL-1β Levels in CCI Rats Following Sitagliptin and GLP-1 Receptor Blockade Treatment. Spinal cord IL-1β levels were measured in rats subjected to chronic constriction injury (CCI) and treated with vehicle, sitagliptin (20 mg/kg, oral gavage), Exendin (9–39) (160 µg/kg, IP), or their combination for 15 consecutive days. Spinal cord tissues were collected on day 15 following CCI induction for IL-1β determination. Data are presented as mean ± SEM (n = 7 per group). *P < 0.05, **P < 0.01, ***P < 0.001 vs. Sham; #P < 0.05, ##P < 0.01, ###P < 0.001 vs. CCI; &P < 0.05, &&P < 0.01, &&&P < 0.001 vs. CCI + sitagliptin.

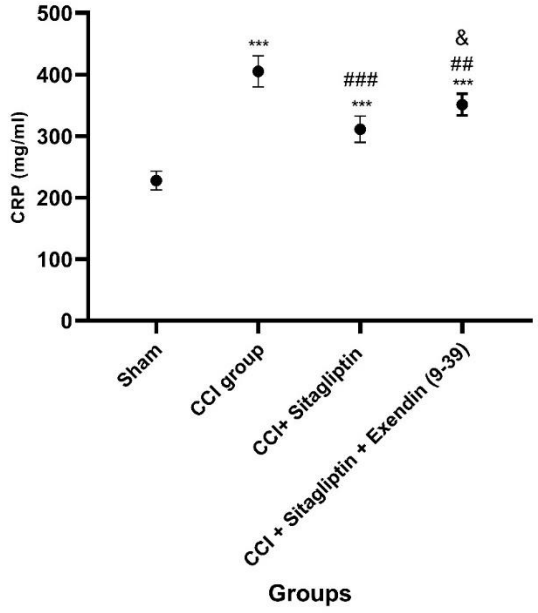

Figure 6. Assessment of Spinal Cord CRP Levels in CCI Rats Following Sitagliptin and GLP-1 Receptor Blockade Treatment. Spinal cord CRP levels were measured in rats subjected to chronic constriction injury (CCI) and treated with vehicle, sitagliptin (20 mg/kg, oral gavage), Exendin (9–39) (160 µg/kg, IP), or their combination for 15 consecutive days. Spinal cord tissues were collected on day 15 following CCI induction for CRP determination. Data are presented as mean ± SEM (n = 7 per group). *P < 0.05, **P < 0.01, ***P < 0.001 vs. Sham; #P < 0.05, ##P < 0.01, ###P < 0.001 vs. CCI; &P < 0.05, &&P < 0.01, &&&P < 0.001 vs. CCI + sitagliptin.

Histopathological Changes Induced by Sitagliptin and GLP-1 Receptor Blockade in the CCI Model

Histopathological analysis revealed significant sciatic nerve injury and inflammation in rats subjected to chronic constriction injury (CCI). In the CCI group, extensive inflammatory cell infiltration (white arrows) and marked axonal degeneration with disruption of nerve fiber architecture (blue arrows) were observed, confirming severe peripheral nerve injury. Treatment with sitagliptin (20 mg/kg, oral gavage) significantly attenuated these pathological alterations, as evidenced by reduced inflammatory infiltration, preserved nerve fiber architecture, and decreased axonal degeneration compared with the untreated CCI group. In contrast, co-administration of sitagliptin and Exendin (9–39) resulted in moderate to severe inflammatory infiltration and axonal degeneration, indicating significantly diminished neuroprotection (Figure 7).

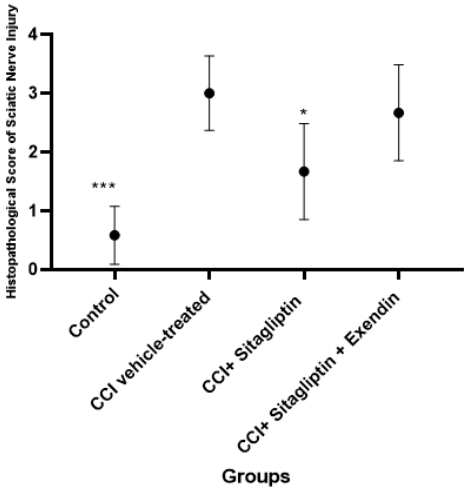

Figure 7. Assessment of Histopathological Injury Scores in the Sciatic Nerve Following Chronic Constriction Injury (CCI) and Treatment with Sitagliptin and GLP-1 Receptor Blockade. Histopathological injury was evaluated in hematoxylin and eosin (H&E)-stained sciatic nerve sections obtained from rats subjected to chronic constriction injury (CCI) and treated with vehicle, sitagliptin (20 mg/kg, oral gavage), Exendin (9–39) (160 µg/kg, IP), or their combination for 15 consecutive days. Histopathological injury scores were determined using predefined morphological criteria. Data are presented as mean ± SEM (n = 7 per group). Statistical analysis was performed using one-way ANOVA followed by Bonferroni's multiple comparisons test. P < 0.05 was considered statistically significant.

Discussion

The present study demonstrates that CCI-induced neuropathic pain is associated with enhanced thermal and mechanical hypersensitivity, elevated pro-inflammatory cytokines (IL-1β and CRP),

reduced motor nerve conduction velocity (MNCV), and pronounced structural damage to the sciatic nerve, characterized by intense inflammatory infiltration and marked axonal degeneration with disruption of nerve fiber architecture in histopathological analyses.

Treatment with sitagliptin significantly alleviated pain behaviors, improved MNCV, and notably attenuated both inflammatory markers and structural nerve damage. Histopathological examination revealed that sitagliptin treatment promoted morphological recovery, as evidenced by reduced inflammatory infiltration and preserved nerve fiber architecture compared to the untreated CCI group. Importantly, pharmacological inhibition of GLP-1 receptor activity using Exendin (9–39) significantly attenuated the analgesic, anti-inflammatory, and neuroprotective efficacy of sitagliptin, with histological analysis revealing persistent inflammatory infiltration and extensive axonal degeneration in this group. These findings indicate that the therapeutic effects of sitagliptin are, at least in part, mediated through GLP-1 receptor signaling, while the observation that GLP-1 blockade did not entirely abolish structural preservation suggests that additional GLP-1–independent pathways may contribute to its neuroprotective profile. Collectively, these results elucidate the mechanisms underlying the neuroprotective actions of sitagliptin and highlight its potential as a therapeutic strategy for neuropathic pain management, warranting further clinical investigation.

Sitagliptin has been shown to exert neuroprotective effects by reducing oxidative stress and neuroinflammation, and by preventing neuronal apoptosis (28, 29). By inhibiting DPP-4, Sitagliptin increases GLP-1 levels (30), and activation of the GLP-1 receptor mediates many of its neuroprotective effects (16). Activation of GLP-1R supports neuronal survival, enhances mitochondrial function, promotes neurogenesis, reduces oxidative stress and neuroinflammation, and inhibits apoptotic pathways (31, 32). GLP-1R activation also exerts anti-inflammatory effects by lowering pro-inflammatory cytokines and reducing immune cell activation, thereby promoting nerve survival and regeneration (33, 34). By reducing inflammation, GLP-1 receptor signaling contributes to neuroprotection and supports nerve survival and regeneration (33, 34). GLP-1R agonists rapidly improve nerve function, increase myelinated fiber size and intraepidermal nerve fiber density, and reduce Schwann cell apoptosis (32). The neuroprotective effects of GLP-1 receptor signaling are not limited to direct neuronal actions but also involve modulation of multiple cell types (35). Activation of GLP-1R suppresses microglia-mediated neuroinflammation, attenuates macrophage senescence and inflammatory mediator production, and promotes remyelination and axonal regeneration (36). These coordinated cellular responses may explain the observed improvements in motor nerve conduction velocity and sciatic nerve histology following sitagliptin treatment in the present study. Oxidative stress and mitochondrial dysfunction are also recognized as key contributors to the pathogenesis of neuropathic pain and peripheral nerve degeneration following chronic nerve injury (37). Excessive generation of reactive oxygen species impairs mitochondrial bioenergetics, promotes lipid peroxidation, and amplifies inflammatory signaling, ultimately leading to neuronal dysfunction and axonal degeneration (37). Previous studies have shown that GLP-1 receptor activation improves mitochondrial function, restores mitochondrial membrane potential and respiration, reduces oxidative stress, and exerts cytoprotective effects in both neuronal and non-neuronal cells (38). Although oxidative stress markers and mitochondrial function were not directly evaluated in the present study, these

mechanisms may have contributed to the observed improvements in behavioral responses, nerve conduction, and histopathological outcomes following sitagliptin treatment. Future studies incorporating oxidative stress biomarkers and mitochondrial functional analyses are warranted to further clarify these potential mechanisms. Beyond GLP-1–dependent mechanisms, Sitagliptin may exert neuroprotective effects via alternative pathways. For example, Ritu Soni et al. (2025) reported that Sitagliptin activates the PI3K/AKT and Nrf2 pathways and reduces alpha-synuclein accumulation in Parkinson's disease models independently of GLP-1 signaling (39). Additional DPP-4 substrates, including stromal cell-derived factor 1 alpha (SDF-1α) (40), neuropeptide Y (NPY) (36), glucose-dependent insulinotropic peptide (GIP) (41), and, to a lesser extent, Substance P and brain natriuretic peptide (BNP) (42), have also been shown to exert neuroprotective effects, supporting the notion that DPP-4 inhibition enhances neuroprotection through multiple pathways beyond GLP-1. SDF-1α/CXCR4 signaling, for instance, may contribute to nerve repair by promoting neural progenitor migration, angiogenesis, and structural preservation, highlighting the multi-faceted mechanisms of DPP-4 inhibition in neuropathic conditions (43, 44). Collectively, GLP-1 receptor signaling appears to be a major contributor to the neuroprotective effects of sitagliptin, as pharmacological blockade of GLP-1R partially reversed its beneficial effects (15, 45), additional GLP-1–independent pathways provide complementary benefits, enhancing its therapeutic potential in neuropathic pain and nerve regeneration.

Conclusion

In summary, our study demonstrates that Sitagliptin significantly alleviates CCI-induced neuropathic pain, improves nerve conduction, reduces inflammation, and preserves nerve structure. These findings support an important contribution of GLP-1 receptor signaling to the neuroprotective effects of sitagliptin; however, additional GLP-1R-independent mechanisms are also likely to be involved. These findings suggest that additional GLP-1-independent mechanisms may contribute to sitagliptin-mediated neuroprotection, potentially involving pathways such as PI3K/AKT, Nrf2 activation, and modulation of other DPP-4 substrates reported in previous studies. Overall, these results highlight Sitagliptin's multi-faceted neuroprotective potential and its promise as a therapeutic agent for mitigating neuropathic pain and supporting nerve repair and regeneration.

Limitations and Future Directions

Several limitations of the present study should be acknowledged. First, although co-administration of Exendin (9–39) supported the involvement of GLP-1 receptor signaling, direct assessment of GLP-1R expression or downstream signaling pathways, such as cAMP/PKA or PI3K/Akt, was not performed. Second, oxidative stress, mitochondrial function, and glial activation were not directly evaluated, limiting mechanistic insight into the pathways underlying sitagliptin-mediated neuroprotection. Third, the study was limited to a single dose of sitagliptin and a single experimental time point following CCI, precluding evaluation of dose-response relationships and long-term therapeutic efficacy. Finally, because this investigation was conducted in an experimental rat model, caution is warranted when extrapolating these findings to human neuropathic pain. Future studies incorporating molecular pathway analyses, multiple dosing regimens, and longer follow-up periods are needed to further define the mechanisms and translational potential of sitagliptin.

Mechanistic and Translational Relevance

Peripheral nerve injury-induced neuropathic pain remains a major therapeutic challenge due to the limited availability of disease-modifying treatments. The present study provides mechanistic evidence that sitagliptin exerts neuroprotective and anti-inflammatory effects in a chronic constriction injury model of neuropathic pain. Pharmacological blockade of GLP-1 receptor signaling using Exendin (9–39) partially attenuated the beneficial effects of sitagliptin on pain-related behaviors, motor nerve conduction velocity, inflammatory responses, and sciatic nerve morphology, suggesting that GLP-1R signaling contributes to sitagliptin-mediated neuroprotection. However, the incomplete reversal of these effects indicates the involvement of additional GLP-1R-independent mechanisms.

From a translational perspective, these findings expand the potential therapeutic relevance of sitagliptin beyond its established metabolic indications and suggest that DPP-4 inhibition may represent a pharmacological strategy for modulating neuroinflammation and promoting peripheral nerve recovery. Given the clinical availability and established safety profile of sitagliptin, further investigations are warranted to determine whether its neuroprotective properties can be translated into clinical settings, particularly in patients with peripheral neuropathies associated with metabolic or non-metabolic nerve injury.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Somayeh Delfani: Investigation, Data curation. Farzaneh Bagheri: Conceptualization, Methodology, Methodology, Writing – original draft. Ali Rashidian-Rashidabadi: Investigation, Data curation, Methodology, Histopathological analysis. Sanaz Mokhtari: Conceptualization, Methodology. Samad Darabian: Formal analysis, Data interpretation. Abolfazl Abbaszadeh: Conceptualization, Methodology, Investigation, Supervision, Project administration, Writing – review and editing. All authors have read and approved the final version of the manuscript.

Ethics Statement

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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