

## Retraction

# Retracted: Lidocaine Ameliorates Diabetic Peripheral Neuropathy in Streptozotocin-Induced Diabetic Rats through Modulating the c-Jun Signaling Pathway

### Contrast Media & Molecular Imaging

Received 25 July 2023; Accepted 25 July 2023; Published 26 July 2023

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

- (1) Discrepancies in scope
- (2) Discrepancies in the description of the research reported
- (3) Discrepancies between the availability of data and the research described
- (4) Inappropriate citations
- (5) Incoherent, meaningless and/or irrelevant content included in the article
- (6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their


agreement or disagreement to this retraction. We have kept a record of any response received.

### References

- [1] J. Luo, D. Wu, Q. Wu et al., "Lidocaine Ameliorates Diabetic Peripheral Neuropathy in Streptozotocin-Induced Diabetic Rats through Modulating the c-Jun Signaling Pathway," *Contrast Media & Molecular Imaging*, vol. 2022, Article ID 1888153, 9 pages, 2022.

## Research Article

# Lidocaine Ameliorates Diabetic Peripheral Neuropathy in Streptozotocin-Induced Diabetic Rats through Modulating the c-Jun Signaling Pathway

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Received 1 June 2022; Revised 27 June 2022; Accepted 8 July 2022; Published 17 August 2022

Academic Editor: Yuvaraja Teekaraman

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As one of the common complications of diabetes mellitus (DM), Diabetic Peripheral Neuropathy (DPN) threatens human lives seriously. Emerging evidences have confirmed the protective effects of lidocaine on DPN. However, the possible role and underlying mechanisms of lidocaine in DPN have not been clarified. In this study, the potential role of lidocaine in DPN is explored, and the possible mechanisms are investigated. The rat DPN model is constructed through administration of streptozotocin (STZ, 60 mg/kg). All rats are randomly divided into four groups, including the control group, DPN group, lidocaine (3.78 mg/time) group, and lidocaine combined with the SP600125 (15 mg/kg) group. Mechanical threshold, thermal latency, and blood glucose of rats before and after treatment are detected, and Nerve Conduction Velocity (NCV) is assessed. Moreover, qRT-PCR and western blot assays are carried out to determine the expressions of the c-Jun signaling pathway. The experimental results demonstrate that lidocaine remarkably downregulates the mRNA and protein expressions of the c-Jun signaling pathway in serum and DRGs induced with DPN. Besides, lidocaine combined with SP600125 can obtain better effects than lidocaine alone. It is clearly evident that lidocaine has a certain therapeutic effect on DPN.

## 1. Introduction

With the development of economy and the change of life style, diabetes has gradually become a common metabolic disease [1]. As one of the chronic complications of diabetes, Diabetic Peripheral Neuropathy (DPN) is a serious threat to human life. Epidemiological investigation shows that the incidence rate of DPN can reach 30%–90% and is increasing year by year [2]. According to the statistics of the International Diabetes Federation, the number of people with diabetes nephropathy is expected to increase to nearly 500 million by 2030 [3]. DPN patients have different degrees of clinical manifestations, such as numbness, electric shock, pain, muscle weakness, or atrophy [4]. In severe cases, DPN can lead to lower limb ulcers and even amputations. The

disease lasts for a long time and is difficult to cure. It has a great impact on the patient's life [5]. At present, the pathogenesis of DPN is not clear, resulting in many patients' failure to diagnose and treat in time [6]. Therefore, the research on DPN has a certain potential value. The first step of DPN treatment is to strictly control blood glucose to prevent metabolic disorder caused by persistent hyperglycemia in the body. This will fundamentally prevent and suppress the occurrence and development of DPN. Once neuropathic pain occurs, only by controlling the fluctuation of blood glucose, the reversal of symptoms is very limited. Patients need comprehensive treatment, such as drug therapy, nerve block therapy, rehabilitation therapy, and spinal cord stimulation (SCS) [7, 8]. However, the drug resistance of patients with DPN is low [9]. Once spinal

infection occurs, it will be disastrous for patients [10]. Therefore, seeking a safe, effective, minimally invasive, and low-cost treatment is a hot issue in current research.

Lidocaine is a typical local anesthetic that can act on nerves [11]. It can not only increase the threshold potential of nerve impulse and inhibit the rising speed of action potential depolarization but also prolong the refractory period of action potential to achieve the effect of local anesthesia [12]. Studies have shown that intravenous infusion of lidocaine can produce analgesic effects, and the possible mechanism is to block peripheral and central voltage-gated sodium channels [13]. During neuropathic pain, the sodium channel on the peripheral nerve cell membrane is abnormally highly expressed, and the injured peripheral nerve can mediate the ectopic discharge of dorsal root ganglions (DRGs) and adjacent neurons [14]. Intravenous infusion of lidocaine inhibited the abnormal discharge of the damaged peripheral nerve and produced analgesic effects [15]. Previous studies have shown that lidocaine had positive effects on DPN progression. For instance, lidocaine exhibited better effects on DPN. Besides, lidocaine resulted in a 51% pain reduction 60 to 120 min after infusion initiation, as assessed on a 0 to 10 numerical rating scale [16]. Lidocaine administration reduced mean neuropathic pain symptom inventory paresthesia/dysesthesia scores [17]. However, the detailed role and underlying mechanisms remain unclear.

The c-Jun N-terminal Kinase (JNK) family is a serine/threonine protein kinase and a member of the Mitogen Activated Protein Kinase (MAPK) superfamily in mammals [18]. JNK phosphorylation activates extracellular signal-regulated kinase to cause the proliferation and activation of microglia, further secreting IL- $\beta$ , TNF- $\alpha$ , and other cytokines to promote the inflammatory response after injury [19]. It is found that the increase of inflammatory factor levels can lead to the abnormal activation of the JNK signal transduction pathway, cause pathological processes such as apoptosis, insulin resistance, inflammatory response, and abnormal expression of downstream target genes, and then lead to peripheral neuropathy, which plays an important role in the formation of DPN [20]. Recent studies have confirmed that peripheral nerve axon injury can induce long-term activation of JNK in rat DRGs [21]. The phosphorylated JNK and c-Jun in the sciatic nerve nuclei of STZ-induced diabetic rats are increased significantly, and the phenotype of neurons is changed by affecting the transcription of c-Jun, suggesting that activation of the c-Jun signal transduction pathway might be one of the pathogenesises of DPN [22, 23]. However, there is no report that the effect of lidocaine on DPN is related to the expression of the c-Jun signaling pathway. Therefore, the purpose of this study is to observe the therapeutic effect of lidocaine on DPN rats and then to explore the correlation between the effect of lidocaine on the c-Jun signal pathway and DPN treatment [24]. The research results can provide a new experimental basis for lidocaine in the treatment of DPN.

This paper is organized as follows: Section 2 discusses the related work, and Section 3 presents DPN model and measurements. In Section 4, the results and analysis are

proposed. Finally, some concluding remarks are made in Section 5.

## 2. Related Work

At present, there is no ideal DPN animal model. The DM animal model induced with SZT is usually used for DPN study at home and abroad [25, 26]. It has been generally agreed that the blood glucose value is greater than 16.65 mmol/L as a model for DM rats [27]. Electrophysiological examination is a sensitive index for early diagnosis of DPN. Clinically, many patients with DPN have obvious slowing of NCV before obvious motor and sensory disorders [28]. In the experimental DPN study, it has been found that the NCV has slowed down significantly in the early stage of DM. Motor nerve conduction velocity (MNCV), which reflects the functional state of sciatic nerve movement, is the most commonly used observation index in the study of experimental DPN [29].

Recently, the beneficial effect of lidocaine on the treatment of DM has attracted more and more attention [30]. Some literature works indicate that lidocaine has significant improvement in DPN. For instance, one of the causes of neuropathic pain is the release of inflammatory cytokines. Sommer et al. [31] showed that intravenous use of lidocaine can inhibit the inflammatory response, block the nerve conduction of the injured tissues, and weaken the neurogenic inflammation so as to suppress peripheral and central sensitization. Besides, lidocaine inhibited Voltage-Gated Calcium Channel (VGCC), Voltage-Gated Sodium Channel (VGSC), potassium channel, N-methyl-D-aspartic acid receptor (NMDA receptor), G protein pathway, and glycine system so as to reduce the discharge of ectopic neurons, which further inhibited peripheral and central sensitization, relieved hyperalgesia, and regulated inflammatory responses [32]. The diabetic DRGs are very fragile, which is an important part of DPN [33].

JNK family is a serine/threonine kinase, also known as stress-activated protein kinase (SAPK), belonging to the MAPK family found in mammals [34]. Under the conditions of high glucose and oxidative stress, the main biological effects of the JNK signal transduction pathway are that JNKs/SAPK kinases bind to the delta domain of c-Jun protein, rapidly phosphorylate the ser63 and ser73 sites of c-Jun, and enhance the transcriptional activation function of c-Jun so as to activate the expression of related downstream genes, leading to a series of responses related to nerve regeneration and repair [35, 36]. Many experiments have confirmed the relationship between DPN and JNK/SAPK [37]. For instance, immunohistochemistry and western blot confirmed that the activities of extracellular signal-regulated kinase (ERK) and JNK are increased, and the phosphorylation of neurofilament is also enhanced in the sensory neurons of spontaneously DM rats and STZ-induced rats. The neurofilament is the substrate of ERK and JNK, suggesting that phosphorylation of neurofilament protein induced by ERK and JNK might be the pathogenesis of diabetic sensory neuropathy [38]. In addition, three MAPK pathways, including ERK1/2, JNK, and p38 in DRGs of DM rats are

activated [39–42]. As the most important nuclear transcription factor of the JNK/SAPK signal transduction pathway, C-Jun has been confirmed closely related to neuronal apoptosis under pathological conditions [43–46]. Zhuang et al. [47] detected the expression of c-Jun in DRG after spinal nerve injury (SNL) and found that c-Jun expression in L5 DRG is upregulated, suggesting that c-Jun is a marker of the molecular level of peripheral nerve injury [41]. In addition, Watson et al. [48] found that the levels of c-Jun are increased selectively during the apoptosis of sympathetic neurons after removing the NGF arch. Moreover, c-Jun promoted the apoptosis of damaged neurons by down-regulating Atf2 and JunD [49]. Some findings suggested that c-Jun mediated DPN progression through activating the cascade reaction of the JNK/SAPK signal transduction system.

### 3. DPN Model and Measurements

**3.1. Experimental Animals.** A total of 40 Sprague-Dawley (SD) rats (200 g, sex in half) are purchased from the experimental center of Guizhou Medical University, and all animals are housed under standard environmental conditions at controlled temperature ( $22 \pm 2^\circ\text{C}$ ), humidity ( $50 \pm 10\%$ ), and light (12 h light/dark cycle) with free access to standard diet and water. All procedures for animal care and use are approved by the ethics committee of Guizhou Medical University.

**3.2. Establishment of the DPN Model in Rats.** SD rats are randomly divided into four groups, including the control group, DPN group, lidocaine group, and lidocaine combined with the SP600125 group, with ten rats in each group. Lidocaine is administered at the doses of 3.78 mg/time (once a day, 5 times), and SP600125 is administered at the doses of 15 mg/time (one time every two days, 3 times). The control group and DPN group are given equal volume of distilled water by gavage once a day. In addition to the control group, rats in each group are single-injected intraperitoneally with streptozotocin (STZ, 60 mg/kg). After 2 days, the tail vein blood of rats is collected, and the blood glucose is measured. At 7, 14, 21, and 28 days after STZ injection, the right hind paw of rats is stimulated with von Frey filaments with different labels to induce a mechanical foot retraction reaction. The mechanical threshold (MWT) of the right hind paw of rats is measured. If MWT is decreased by more than 50% on the 28th day, the DPN model is successfully prepared.

**3.3. Measurement of Pain Behaviors.** MWT and thermal latency (TML) are measured as described previously [24]. In brief, the BME-410C automatic thermal pain stimulator is used to irradiate the plantar part of rats. The time from the beginning of irradiation to the occurrence of the positive reaction in rats is recorded. The measurement is repeated three times with an interval of 5 min each time, and the average value is taken as TWL. Rats from different groups are placed in the plexiglass box with barbed wire at the

bottom. After 15 min of adaptation, the ciliary stimulation needle is used to vertically act on the plantar surface of the hind limb and bend the ciliary needle for 2–4 s until the foot retraction avoidance reaction occurred. From the first positive reaction, the measurement is repeated for 5 times, with an interval of 5 min. 50% MWT is calculated by the up and down method.

**3.4. Measurement of Nerve Conduction Velocity (NCV).** After successful anesthesia, the rats are fixed in prone position, and the right sciatic nerve is bluntly separated with a glass minute needle. The conduction velocity of the sciatic nerve is measured by the Medlab biological signal acquisition and processing system.

**3.5. Transmission Electron Microscopy (TEM) Assay.** The DRGs are dissected, sampled in 2.5% glutaraldehyde ( $1 \text{ mm} \times 1 \text{ mm} \times 3 \text{ mm} - 4 \text{ mm}$ ), and stored at  $4^\circ\text{C}$ . The prepared samples are fixed with 1% osmic acid and embedded with Epon812. Afterwards, ultrathin slice is prepared and stained with uranyl acetate and lead citrate. The ultrastructure of DRGs is observed by TEM (FEI TECNAI G20, USA).

**3.6. RT-qPCR.** After extracting total RNA from serum and DRG tissues of rats in different groups, cDNA is prepared with RNA by the RNeasy plus micro kit, as the starting material of RT-qPCR was carried out using the Step One System (Life Technologies Corp). Primer Premier software 4.0 (Premier, Canada) designed sequences of all primers, as shown in Table 1.

**3.7. Western Blotting.** Protein from serum and DRG tissues of rats in different groups are extracted and measured with the BCA kit (Beyotime Biotechnology, China). The protein is transferred to the PVDF membrane after 10% SDS-PAGE gel electrophoresis. After enclosing with 5% skimmed milk, the antibodies including anti-TNF- $\alpha$  (bs-10802R, 1 : 2, 000, Bioss, China), anti-IL-6 (bs-4539R, 1 : 2, 000, Bioss, China), anti-MKK4 (bs-1977R, 1 : 2, 000, Bioss, China), anti-p-MKK4 (bs-3392R, 1 : 2, 000, Bioss, China), anti-p-JNK (bsm-52462R, 1 : 2, 000, Bioss, China), anti-p-c-Jun (bs-12913R, 1 : 2, 000, Bioss, China), and anti-GAPDH (bs-0755R, 1 : 2, 000, Bioss, China) are incubated overnight. Secondary resistance (1 : 4,000, SA00004-10, Proteintech, China) is subsequently incubated at  $37^\circ\text{C}$ . Finally, ECL (Millipore, USA) is utilized to detect protein blots, whereas ImageJ software (NIH, version 4.3) is adopted for quantification.

**3.8. Statistical Analysis.** The average  $\pm$  standard deviation (SD) represents data from three repetitions. GraphPad Prism 8.0 software (GraphPad Software, Inc.) is applied. The comparison between the two groups is conducted by the *t*-test, and the group comparison is employed by single-factor ANOVA and the Tukey posttest.  $P < 0.05$ , the difference is statistically significant.

TABLE 1: Primer sequences.

Gene name	Primer sequences
TNF- $\alpha$	F: 5'-ATGTGGAAGTGGCAGAGGAG-3' R: 5'-CGAGCAGGAATGAGAAGAGG-3'
IL-6	F: 5'-AGACTTCACAGAGGATACCACCCAC-3' R: 5'-CAATCAGAAATGCCATTGCACAA-3'
MKK4	F: 5'-GCGGAGTAGTGATTGCCCAT-3' R: 5'-GATCCAACAGTCGCCCTCTC-3'
JNK	F: 5'-CAAGGACTGCAGGAACGAGT-3' R: 5'-TAGCCCATGCCGAGAATGAC-3'
Jun	F: 5'-ACATGCTCAGGGAACAGGTG-3' R: 5'-GCGTTAGCATGAGTTGGCAC-3'
GAPDH	F: 5'-TGCTGAGTATGTCGTGGAGTC-3' R: 5'-TGCTGACAATCTTGAGGGAG-3'

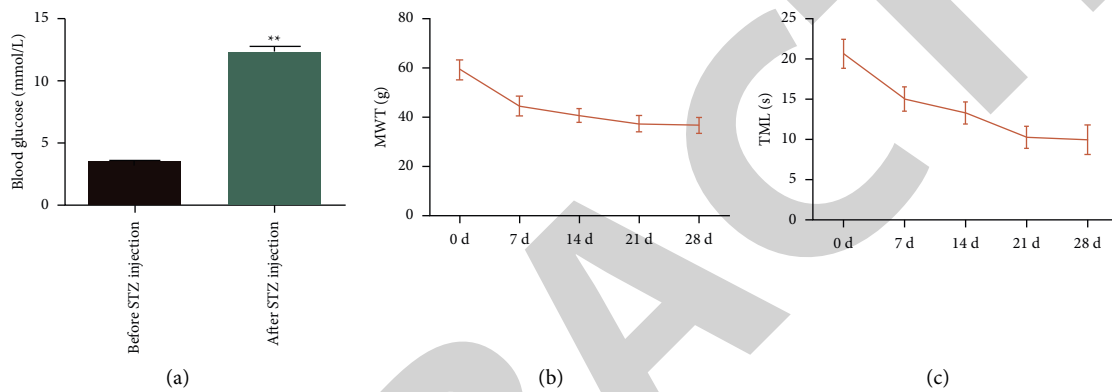


FIGURE 1: Construction of the rat DPN model: (a) the blood glucose in rats before and after STZ injection. \*\* $P < 0.01$  vs. blood glucose before STZ injection; (b) MWT in rats after STZ injection at 0, 7, 14, 21, and 28 days; (c) TML in rats after STZ injection at 0, 7, 14, 21, and 28 days.

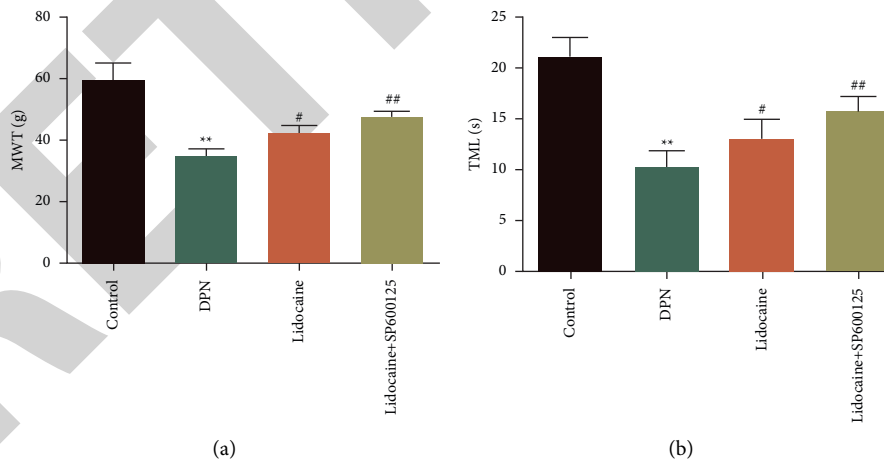


FIGURE 2: Continued.

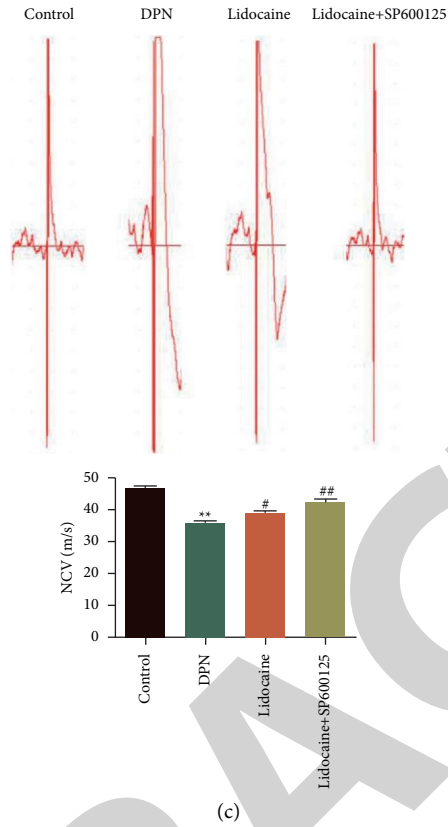


FIGURE 2: Effects of lidocaine on pain behaviors and NCV in DPN rats: (a) MWT; (b) TML; (c) NCV in DPN rats administrated with lidocaine or lidocaine combined with SP600125.

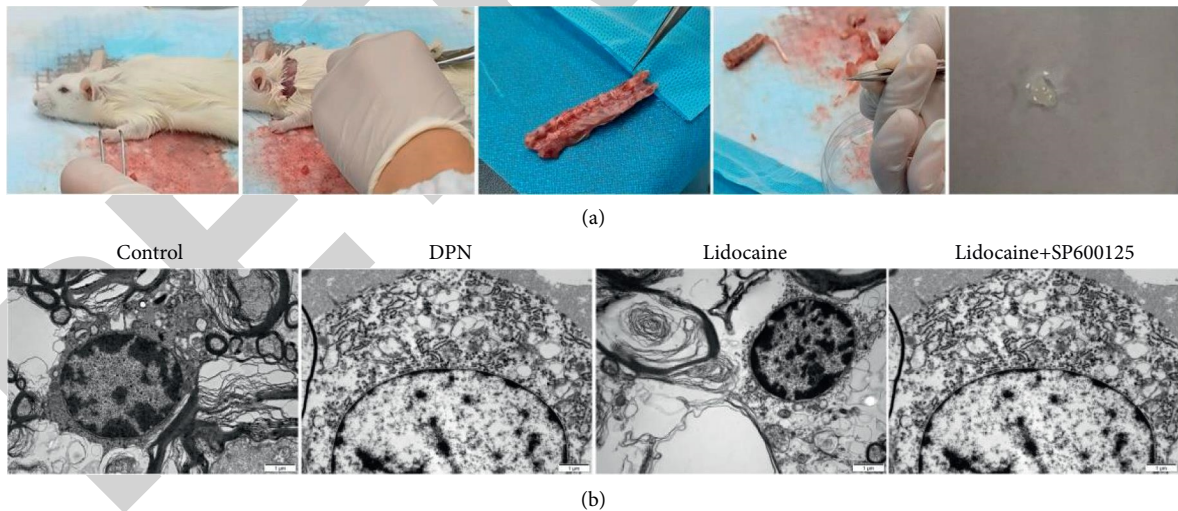


FIGURE 3: Effects of lidocaine on the ultrastructure of DRGs in DPN rats: (a) sampling of DRGs; (b) TEM is carried out to observe the effects of lidocaine on the morphological changes of DRGs from different groups.

#### 4. Results and Analysis

**4.1. Effects of Lidocaine on Pain Behaviors and NCV in DPN Rats.** To explore the possible role of lidocaine in the development and progress of DPN, firstly the rat DPN model is constructed. Figure 1 shows the construction of the rat DPN model. Figure 1(a) demonstrates the blood glucose in rats

before and after STZ injection. Figure 1(b) shows the MWT in rats after STZ injection at 0, 7, 14, 21, and 28 days. Besides, TML in rats after STZ injection at 0, 7, 14, 21, and 28 days can be observed in Figure 1(c). Compared with the control group, the blood glucose in DPN rats is greater than 16.7 mmol/L. At 7, 14, 21, and 28 days after STZ injection, the MWT and TML are obviously decreased in DPN rats. These data suggested

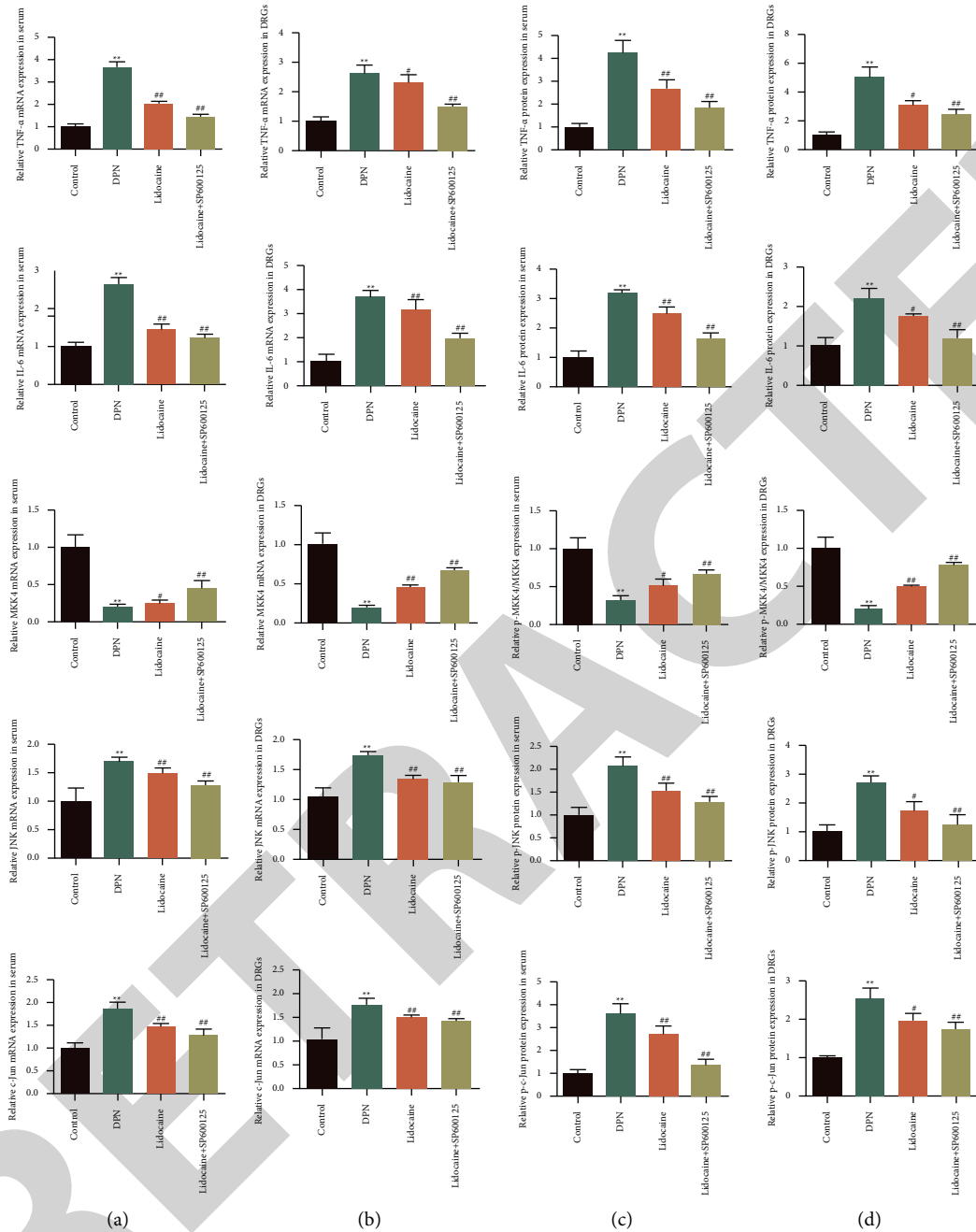


FIGURE 4: Effects of lidocaine on the expressions of the c-Jun signaling pathway in DPN rats: (a) the mRNA expressions of the c-Jun signaling pathway in serum from different groups are determined by qRT-PCR analysis; (b) the protein expressions of the c-Jun signaling pathway in serum from different groups are determined by western blot analysis; (c) the mRNA expressions of the c-Jun signaling pathway in DRGs from different groups are determined by qRT-PCR analysis; (d) the protein expressions of the c-Jun signaling pathway in DRGs from different groups are determined by western blot analysis.

that the DPN model is successfully constructed. Figure 2 shows the effects of lidocaine on pain behaviors and NCV in DPN rats. After treatment with lidocaine, the MWT and TML are remarkably improved shown in Figures 2(a) and 2(b). In

addition, the NCV in rats from different groups is also analyzed. As can be observed in Figure 2(c), compared with the control group, the NCV of DPN rats decreased significantly, and lidocaine partially restored this phenomenon.



**4.2. Effects of Lidocaine on the Ultrastructure of DRGs in DPN Rats.** To observe the effects of lidocaine on the morphological changes of DRGs, as shown in Figure 3(a), TEM is carried out. As can be observed in Figure 3(b), in the control group, on the cross section of DRGs, the myelin sheath is dense, uniform, structurally complete, and regular, showing a concentric lamellar structure alternating light and dark, and the axon had no atrophy and swelling. In the DPN group, myelinated nerve fibers showed loose structure, expanding inward (axon surface) and outward (interstitial surface), the structure of myelin lamina is unclear and arranged in disorder, and some laminae are broken and separated, showing serious demyelination. The arrangement of microfilaments and microtubules in axons is disordered, and atrophy is obvious. After treatment with lidocaine, these phenomena are obviously improved. These data suggested that lidocaine can improve the ultrastructure of DRGs in DPN rats.

**4.3. Effects of Lidocaine on the Expressions of the c-Jun Signaling Pathway in DPN Rats.** The C-Jun signaling pathway exerts essential effects on DPN progression. Whether lidocaine regulated the c-Jun signaling pathway in DPN is unclear. qPCR and western blot assays are adopted to evaluate the expression levels of the c-Jun signaling pathway in serum and DRGs. Figure 4 shows the effects of lidocaine on the expressions of the c-Jun signaling pathway in DPN rats. In Figure 4(a), the mRNA expressions of the c-Jun signaling pathway in serum from different groups are determined by qRT-PCR analysis. The protein expressions of the c-Jun signaling pathway in serum from different groups are determined by western blot analysis, as shown in Figure 4(b). Figure 4(c) demonstrates that the mRNA expressions of the c-Jun signaling pathway in DRGs from different groups are determined by qRT-PCR analysis. In addition, the protein expressions of the c-Jun signaling pathway in DRGs from different groups are determined by western blot analysis, as shown in Figure 4(d). Compared with the control group, the mRNA (TNF- $\alpha$ , IL-6, JNK, and c-Jun) and protein (TNF- $\alpha$ , IL-6, p-JNK, and p-c-Jun) expression levels are notably increased, while the mRNA (MKK4) and protein (p-MKK4/MKK4) expression levels are notably decreased in DPN rat serum and DRGs. As expected, lidocaine partially restored the expressions of the c-Jun signaling pathway induced with DPN. These data suggested that lidocaine can suppress the c-Jun signaling pathway in DPN rats.

**4.4. Effects of Oflidocaine on DPN Progression Mediated with the c-Jun Signaling Pathway.** Based on the above results, whether lidocaine exhibited its functional role in DPN mediated with the c-Jun signaling pathway is further investigated. SP600125, a c-Jun inhibitor, is used to treat DPN rats combined with lidocaine. Based on the results of MWT and TWL, lidocaine combined with SP600125 improves the MWT and TWL relative to the lidocaine group. In addition, the data of NCV displayed lidocaine combined with SP600125 increased the NCV compared with the lidocaine

group. Besides, according to the TEM assay, lidocaine combined with SP600125 enhanced the effects of lidocaine alone on the ultrastructure of DRGs in DPN rats. Moreover, the data of qPCR and western blot analysis showed that lidocaine combined with SP600125 further improved the inhibitory effects of lidocaine on the expressions of the c-Jun signaling pathway. It is suggested that lidocaine can exert the protective effects on DPN progression mediated with the c-Jun signaling pathway.

## 5. Conclusions

In this paper, LIDOCAINE ameliorates diabetic peripheral neuropathy in streptozotocin-induced diabetic rats through modulating the c-Jun signaling pathway which is investigated. This study innovatively puts forward that intravenous infusion of lidocaine can improve DPN through reducing inflammatory factors and decreasing the expression levels of c-Jun. The findings can provide a new perspective for the prevention and treatment of DPN. In the future work, we will further study the clinical effect and mechanism of lidocaine and verify the effect of prostaglandin E1 and lidocaine in the treatment of diabetes peripheral neuropathy.

## Data Availability

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Dashou Wang contributed equally to the corresponding author. JinyuLuo, Dedan Wu, and Qianming Wu conceived and designed the experiments. Yan Chen, Yong Gan, and Wenyangming Sun performed most of the experiments. Yiqin Ai, Meng He, and Qiuping Su interpreted all results. XiaohuaZou and Dashou Wang analyzed the data and wrote the manuscript.

## Acknowledgments

The work was supported by the Science and Technology Fund Project of Guizhou Provincial Health Commission (project name: Study on the Mechanism of Lidocaine Injection Inhibiting c-Jun Phosphorylation and Improving Neuropathic Pain, No. gzwkj2021-275) and Science and Technology Fund Project of Guizhou Provincial Health Commission (No. 2021XMSB00031150).

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