

Curcumin alleviates SNI-induced neuropathic pain by regulating the AMPK/PGC-1 α signaling axis in the spinal cord

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Abstract

Rationale:

Neuropathic pain, a chronic and prevalent condition, imposes significant psychological burdens on patients and society. There is an urgent need to improve pain management strategies and develop new analgesic drugs. Traditional Chinese Medicine (TCM) has gained popularity for pain relief. Curcumin (Cur), a phenolic compound derived from the rhizome of *Curcuma longa*, exhibits potent antioxidant, anti-cancer, and anti-inflammatory properties. However, the mechanisms by which Cur alleviates neuropathic pain remain poorly understood, and a comprehensive understanding of its therapeutic effects is still lacking.

Methods

Mice were fed with curcumin once daily at a dose of 25, or 50 mg/kg after SNI for 7 consecutive days. Mechanical allodynia and thermal hyperalgesia were evaluated using von Frey filaments and hot plate test, respectively. The open field test and the rotarod test were used to assess the locomotor activity of mice. The levels of AMPK, p-AMPK, PGC-1 α and TNF- α proteins in spinal cord were analyzed by Western blot. The microglia activation marker Iba-1 was detected by immunofluorescence.

Results

Curcumin administration dose-dependently reduced mechanical allodynia and thermal hyperalgesia induced by SNI and produced no significant effect on the spontaneous locomotor activity of the mice. Curcumin treatment alleviated the SNI-induced downregulation of p-AMPK, PGC-1 α and upregulation of TNF- α protein and inhibited the activation of microglia in the mouse spinal cord. Furthermore, pharmacological inhibition of AMPK activation by Compound C abolished the effect of curcumin.

Conclusions

Our findings indicate that curcumin can alleviate SNI induced neuropathic pain behaviors, this effect might be associated with the regulation of spinal AMPK/PGC-1 α signaling axis, suggesting its potential as a therapeutic strategy for neuropathic pain.

1. INTRODUCTION

Neuropathic pain (NP) is a chronic condition resulting from nerve injury or disease, characterized by hyperexcitability within somatosensory nociceptive circuits that significantly impairs quality of life ^[1]. Current pharmacological treatments such as norepinephrine reuptake inhibitors, tricyclic

antidepressants, pregabalin, and gabapentin are commonly used for symptom relief ^[2]. However, the efficacy of these drugs remains limited. Central sensitization, driven by maladaptive synaptic plasticity coupled with widespread neuroinflammation, amplifies pain hypersensitivity and promotes the spread of neuropathic pain [4, 5]. Throughout the progression of neuropathic pain, activated glial cells release cytokines and other inflammatory mediators, which intensify neuroinflammation and reinforce central sensitization ^[3]. The interplay between central sensitization and neuroinflammation not only exacerbates pain but also complicates its management. Therefore, identifying therapeutic targets that can alleviate neuroinflammation and modulate glial cell activity may be crucial for effective control of neuropathic pain^[4].

Numerous studies have established that adenosine monophosphate-activated protein kinase (AMPK) plays a critical role in regulating cellular metabolism and maintaining mitochondrial homeostasis^[5,6]. It has been further reported that AMPK activation enhances mitochondrial biogenesis ^[7] and suppresses reactive oxygen species (ROS) production across multiple pathological contexts ^[8]. Notably, emerging evidence suggests that AMPK activation may alleviate neuropathic pain by modulating neuroinflammation ^[9] and oxidative stress ^[10]. Moreover, AMPK has been shown to promote mitochondrial biogenesis via activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcriptional coactivator that integrates signaling pathways related to energy metabolism, oxidative stress, and mitochondrial function ^[11,12]. A key function of PGC-1α is its ability to coactivate multiple nuclear receptors, including peroxisome proliferator-activated receptor gamma (PPARγ), as well as other transcription factors ^[13]. More recent studies have indicated that overexpression of PGC-1α can downregulate inflammatory cytokine levels by suppressing the activation of nuclear factor κB (NF-κB) ^[14]. The AMPK/PGC-1α pathway has been implicated in the regulation of neuropathic pain development ^[15,16].

Curcumin, a primary compound derived from the rhizome of *Curcuma longa*, has been consumed for centuries as a culinary spice in curry. Owing to its potent anti-inflammatory properties and ability to suppress the production of inflammatory cytokines, curcumin has been employed in the treatment of various neuroinflammatory and neurodegenerative disorders^[17], including Alzheimer's disease^[18], major depression^[19], and diabetic neuropathy ^[20]. Recent studies have further demonstrated its antinociceptive effects in models of neuropathic and inflammatory pain ^[20,21]. Nevertheless, the precise mechanisms through which curcumin alleviates pain remain unclear and warrant further investigation.

In this study, we aimed to investigate the effects of curcumin on SNI-induced neuropathic pain and the underlying molecular pathways. We mainly focus on the role of the AMPK/PGC-1α axis in the mechanism of the analgesic effects of curcumin to provide more effective treatments for neuropathic pain.

2. MATERIALS AND METHODS

2.1. Animals experiments

All experimental procedures were conducted in accordance with the guidelines of the International Association for the Study of Pain and were approved by the Institutional Animal Care and Use Committee of Hubei No. 3 People's Hospital. Male C57 mice (20–25 g, 5–8 weeks old) were housed under a 12 h/12 h light/dark cycle in a temperature-controlled environment with ad libitum access to food and water.

Forty mice were randomly assigned to four groups (n = 10 per group): control, SNI, SNI + Cur (25, and 50 mg/kg). The dosages of Cur were selected based on previous literature ^[22]. The SNI surgery was performed according to the method described by Decosterd and Woolf ^[23]. Briefly, under isoflurane anesthesia, the right hind leg was sterilized with alcohol, and the hair was clipped. An incision was made at the sciatic tubercle, and the muscle layer was bluntly dissected to expose the sciatic nerve and its three distal branches. The sural nerve was left intact, while the other nerves were ligated and transected (using 6 – 0 silk suture). The muscle layer was then closed, and the skin was sutured. In the control group, the sciatic nerve was exposed but not ligated. All mice received intragastric administration of Cur (C7727, total purity > 94.0%, Sigma), or an equal volume of 0.5% CMC-Na Solution. Behavioral tests were conducted on days 0, 3, 5, 7, 10 and 14 of the experimental time line (as illustrated in Fig. 1).

2.2 Open Field Test

Mice were placed in an open field apparatus (50cm × 50cm × 40cm) for 10 minutes daily for three consecutive days to acclimation. During the test, each mouse was placed in the center of the open field, and its movement was recorded for 5 minutes. The duration of activity in the central and peripheral zones was analyzed using behavioral software (SMART 3.0, Panlab).

2.3 Rotarod Test

Mice were trained on a rotarod apparatus (Yishu, Shanghai) at 20 r·min⁻¹ for two days prior to the experiment. Mice capable of staying on the rod for more than 90 seconds were selected for the formal test to minimize intergroup variability. During the test, the rotation speed was increased from 4 r·min⁻¹ to 40 r·min⁻¹ over 5 minutes. The latency to fall (in seconds) was recorded for each mouse. Each mouse was tested twice, and the average value was calculated.

2.4 Hot -plate test

A hot plate (BIO-CHP, Bioseb, France) was set to 52 ± 0.5°C. Each mouse was placed on the hot plate, and the timer was started. The timer was stopped when the mouse exhibited licking of the hind paw or jumping behavior. The pain threshold latency (in seconds) was recorded. Each mouse was tested three times with 10-minute intervals between trials, and the average value was taken.

2.5 Von Frey test

Mice were placed in a specialized plexiglass chamber with a grid floor for approximately 20 minutes to allow acclimation until they remained relatively calm. The hind paw was stimulated using a series of von Frey filaments (0.16–2.56 g, Stoelting) with logarithmically increasing stiffness, applied perpendicularly to the central plantar surface. A positive response was defined as paw lifting or withdrawal. The up-and-down method was employed to record the positive response rate, and the 50% paw withdrawal threshold was calculated.

2.6 Immunofluorescence Staining for Microglia Activation in Mouse Spinal Cord

After behavioral tests, mice were anesthetized by intraperitoneal injection of 1% sodium pentobarbital (40 mg·kg⁻¹) and perfused with 4% paraformaldehyde. The L4–L6 spinal cord segments were collected and post-fixed for 24 hours, followed by gradient dehydration in 20%–30% sucrose solution. After the tissue sank to the bottom, it was embedded in OTC compound for frozen sectioning. Sections (25 µm thick) were washed with PBS and mounted on glass slides. After blocking with 0.15% Triton X-100 and 0.25% BSA at room temperature for 1 hour, the sections were washed three times with PBS and incubated overnight at 4°C with the following primary antibodies: Iba-1 (1:500, Abcam, ab178846). After washing three times with PBS, the sections were incubated with a fluorescent secondary antibody (goat anti-rabbit, 1:500, Abcam, ab150077) protected from light at room temperature for 1 hour. Following three washes with PBS, the sections were mounted with an anti-fade mounting medium containing DAPI. Images were captured using a confocal microscope, and fluorescence intensity was quantified with Image-Pro Plus 6.0 software.

2.7. Quantitative real-time PCR

Total RNA was extracted from cells using Trizol agent (Invitrogen, Waltham, MA, USA), and complementary DNA (cDNA) was synthesized using the Hifair III 1st Strand cDNA Synthesis Kit (Yeasen Biotechnology, Shanghai, China) according to the manufacturer's instructions. Quantitative real-time polymerase chain reaction (qRT-PCR) was performed using Hieff qPCR SYBR Green Master Mix (Yeasen Biotechnology) on an ABI Prism 7500 Sequence Detection System (Applied Biosystems, Waltham, MA, USA). The primer sequences (Sangon Biotech, Shanghai, China) used were as follows: *Il-4* (forward: 5'-AGATGGATGTGCCAAACGTCCTCA-3'; reverse: 5'-AATATGCGAAGCACCTTGAAGCC-3'), *Il-10* (forward: 5'-A CCTGGTAGAAGTGATGCC CCAGGCA-3'; reverse: 5'-CTATGCAGTTGATGAAGATGTCAAA-3'), *Il-6* (forward: 5'-CCA CGGCCTTCCCTAC-3'; reverse: 5'-AAGTGCATCATCGTTGT-3'), *Il-1β* (forward: 5'-ACTCA TGGCTGTGGAGA-3'; reverse: 5'-TTGTTTCATCTCGGAGCCTGT-3'), *Tnf-α* (forward: 5'-CATCTTCTCAAAATTCGAGTGACAA-3'; reverse: 5'-TGGGAGTAGACAAGGTACAACCC-3'). The relative mRNA expression levels of target genes were normalized to that of ACTB and calculated using the 2^{-ΔΔCt} method. All reactions were performed in triplicate, and each experiment was independently repeated three times.

2.8 Western Blot Analysis of Protein Expression in Mouse Spinal Cord

Fresh mouse spinal cord tissue was homogenized in RIPA lysis buffer and centrifuged at $12,000 \times g$ for 10 minutes at 4°C . Protein concentration was determined using the BCA method. SDS-PAGE was performed using 8%–12% separating gels and 5% stacking gels. A total of 20 μg protein was loaded per lane. Electrophoresis was initially carried out at a constant voltage of 80 V for 20 minutes, followed by 120 V for 60 minutes. Proteins were transferred to a membrane at a constant current of 400 mA for 45 minutes. After transfer, the membrane was blocked with blocking buffer at room temperature for 1 hour and then incubated overnight at 4°C with the following primary antibodies: PGC-1 α (1:500, Abcam, ab313559), AMPK (1:500, Abcam, ab32047), p-AMPK (1:500, Abcam, ab133448), TNF- α (1:500, Abcam, ab183218) and β -Tubulin (1:1000, Abcam, ab18207). The membrane was washed three times with TBST (5 minutes per wash), incubated with HRP-conjugated secondary antibody (1:2000, Abcam, ab288151) at room temperature for 1 hour, and washed again three times with TBST. Finally, the blot was developed using an enhanced chemiluminescence reagent and exposed. Grayscale analysis was performed using ImageJ software.

2.9. Statistical analysis

All statistical analyses were performed using GraphPad Prism version 7.0 (GraphPad Software). Data are presented as mean $\pm$ SEM. Behavioral responses to mechanical stimuli were analyzed using two-way repeated-measures ANOVA followed by Bonferroni post hoc tests. For Western blot and immunofluorescence results, one-way ANOVA followed by Bonferroni post hoc tests was applied for comparisons among multiple groups. Comparisons between two groups were conducted using an unpaired Student's t-test. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Effect of curcumin on mice locomotor activity

The open field and rotarod tests were conducted to evaluate the spontaneous locomotor activity of mice. In the open field test, The total moving distance and duration spent in the center area showed no statistically significant differences across each group ($P > 0.05$; Fig. 2A-C), suggesting that the model induction and curcumin treatments did not affect general locomotor activity in this paradigm. In contrast, in the rotarod test, compared to control group, mice in the SNI group demonstrated a markedly decreased fall latency ($P < 0.01$; Fig. 2D), indicating impaired motor coordination. Administration of Cur (50 mg/kg) significantly reversed this effect, with the fall latency being notably longer than that in the SNI group ($P < 0.05$; Fig. 2D). The low-dose treatment Cur (25 mg/kg), however, failed to produce a significant therapeutic effect on the performance. The above findings indicate that Cur treatment does not exhibit significant central inhibitory effects and does not affect spontaneous locomotor activity in mice. Moreover, it may even ameliorate the motor imbalance induced by SNI.

3.2. Effect of curcumin on mechanical allodynia and thermal hyperalgesia

In comparison to mice in control group, those in the SNI group exhibited significant reductions of the mechanical threshold ($P < 0.01$; Fig. 3A) and thermal latency ($P < 0.01$; Fig. 3B) after sciatic nerve injury, which were throughout the 12-day observation period (from day3 to day14). However, repeated intragastric administration of curcumin (50mg/kg), given during the SNI induction markedly attenuated the mechanical allodynia ($P < 0.05$ on day 7 and 14; Fig. 3A) and thermal hyperalgesia ($P < 0.05$ on day 7 and 10; Fig. 3B) in mice from SNI + Cur (50mg/kg) group. While repeated intragastric administration of curcumin (25mg/kg) only partly attenuated the mechanical allodynia ($P < 0.01$; Fig. 3A) and thermal hyperalgesia ($P < 0.01$; Fig. 3B) development. These results suggested that consecutively administering curcumin (25mg/kg or 50mg/kg) for 7 days might alleviate both mechanical and thermal hyperalgesia induced by SNI dose-dependently.

3.3. Effect of curcumin on spinal microglia activation and inflammation.

Immunofluorescence showed SNI treatment increased the staining of the microglia activation marker Iba-1 in the spinal cord ($P < 0.01$; Fig. 4A and B) compared to the control group. Repeated intragastric administration of curcumin (25mg/kg or 50mg/kg) during SNI induction significantly decreased staining of the microglia activation marker Iba-1 ($P < 0.01$; Fig. 4A and B). Meanwhile, we also employed the Western blot method to detect the expression level of Iba-1 protein in the spinal cord. The results indicated that Iba-1 protein expression level in SNI mice spinal cord were significantly increased compared with the control group ($P < 0.001$; Fig. 4A and B). Curcumin (25mg/kg or 50mg/kg) treatment attenuated this upregulation ($P < 0.01$ and $P < 0.05$ respectively; Fig. 4A and B). The above results indicate that Curcumin could alleviate the activation of spinal microglia induced by SNI in mice.

To further evaluate the anti-inflammatory effects of Curcumin, we measured spinal cytokine mRNA levels in SNI mice. Compared with controls, SNI significantly downregulated the anti-inflammatory cytokines *Il-4* and *Il-10* mRNA levels ($P < 0.01$), while robustly upregulating pro-inflammatory mediators *Il-6*, *Il-1 β* , and *Tnf- α* ($P < 0.01$ or $P < 0.001$). Curcumin treatment (25 and 50 mg/kg) dose-dependently reversed these changes: it restored *Il-4* and *Il-10* expression, and suppressed the elevation of *Il-6*, *Il-1 β* , and *Tnf- α* . These effects were statistically significant versus the SNI group ($P < 0.05$ or $P < 0.01$).

3.4. Effect of curcumin on spinal AMPK/PGC-1 α pathway

To further explore the potential mechanisms of the analgesia effect of curcumin, we conducted

western blot experiments to analyze the levels of spinal AMPK, p-AMPK, PGC-1 α and TNF- α in the spinal cord among all groups. Our results revealed that the SNI treatment significantly decreased the expression levels of spinal p-AMPK, PGC-1 α proteins and increased TNF- α protein ($P < 0.01$; $P < 0.001$; $P < 0.01$; respectively, Fig. 6A and B), but Curcumin (25mg/kg or 50mg/kg) treatment upregulated the protein expressions of spinal PGC-1 α ($P < 0.01$; Fig. 6A and B) and p-AMPK ($P < 0.05$; Fig. 6A and D). However, the total AMPK protein level in the spinal cord showed no significant difference among all

groups ($P > 0.05$; Fig. 6A and C). Moreover, the Curcumin (50mg/kg) treatment also downregulated the protein expressions of spinal TNF- α ($P < 0.01$; Fig. 6A and E).

3.5. AMPK activation mediates the analgesic effect of curcumin

To verify the involvement of AMPK/PGC-1 α signaling in curcumin's analgesia, we pre-treated mice with the AMPK inhibitor Compound C (0.5 $\mu\text{g}/\mu\text{l}$, i.t.) 30min before curcumin administration (50 mg/kg, i.g.). This pre-treatment markedly reversed curcumin's analgesic effect. Specifically, Compound C significantly reduced the improvement in mechanical allodynia ($P < 0.05$; Fig. 7A) and thermal hyperalgesia ($P < 0.05$; Fig. 7B) achieved by curcumin alone. Thus, curcumin's attenuation of SNI-induced hypersensitivity depends on the AMPK activation.

DISCUSSION

Our study demonstrates that curcumin, the principal bioactive compound derived from *Curcuma longa*, effectively alleviates SNI-induced neuropathic pain behaviors. Our key findings indicate that systemic administration of curcumin dose-dependently reversed mechanical allodynia and thermal hyperalgesia, without impairing general locomotor activity. Mechanistically, the analgesic effect of curcumin is associated with the activation of the AMPK/PGC-1 α signaling axis and subsequent neuroinflammation in the spinal cord. This was evidenced by decreased levels of p-AMPK, PGC-1 α , and the pro-inflammatory cytokine TNF- α , alongside inhibited microglial activation. Crucially, the pharmacological blockade of AMPK activation abolished curcumin's analgesia effects, underscoring the central role of this pathway.

Curcumin is a safe phytochemical that elicits a wide range of biological actions like anti-inflammatory, anti-oxidant, anti-thrombotic, immunomodulatory, hepatoprotective, anti-diabetic, anti-tumor, and neuroprotective^[2427] In recent years, the use of Curcumin for pain relief has been increasingly reported. Peripheral or central administration of curcumin exerts a dose-dependent antinociceptive effect in the acute^[28], inflammatory^[29], and neuropathic pain models^[30]. It has been reported that curcumin can alleviate orofacial allodynia and improves cognitive impairment via regulating hippocampal synaptic plasticity^[22], curcumin can also inhibit GSK-3 β activation, increases Nrf2 mediated antioxidant to relieve oxaliplatin-induced neuropathic pain^[31]. Consistent with the other studies, our results demonstrate that oral Curcumin administration alleviates SNI-induced pain behaviors in mice in a dose-dependent manner.

To date, growing evidence has illustrated that neuroinflammation participate in the pathogenesis of chronic pain^[32]. Activation of microglia is regarded as a crucial component of neuroinflammation in the CNS, which provides the first line of defense after injuries or diseases^[33]. Once activated, they release a series of proinflammatory factors^[34]. Research shows that curcumin possesses potent anti-inflammatory effects. The anti-inflammatory effects of curcumin are mediated by down-regulation in the activity of cyclooxygenase-2 (COX-2), inflammasome, and inducible nitric oxide synthase (iNOS)^[35].

Moreover, curcumin also inhibits IL-2, IL-6, IL-8, IL-12, TNF- α , macrophage inhibitory protein (MIP), and the production of monocyte chemoattractant protein-1 (MCP-1) pro-inflammatory cytokines and chemokines^[27]. These biological effects appear to be achieved by curcumin-mediated inhibition of NF- κ B^[36,37]. Our study also finds that curcumin treatment inhibited the pro-inflammatory cytokines TNF- α levels and partially inhibited the activation of microglia in the spinal cord of SNI mice.

Further exploration of the cascade signaling axis involved in Curcumin-mediated microglial polarization illustrated the crucial role of the AMPK/PGC-1 α signaling axis in SNI mice. Recently, studies revealed that AMPK/PGC-1 α signaling pathway activation significantly suppressed LPS-induced neuroinflammation in BV2 cells and mouse primary microglia in vitro by regulating microglial polarization^[38]. In line with this study, we also detected a remarkable decrease in spinal p-AMPK and PGC-1 α levels in SNI mice, and their expression levels were significantly increased after Curcumin treatment. Moreover, the analgesic effect of Curcumin could be notably reversed by the classical AMPK inhibitor Compound C, supporting the hypothesis that spinal AMPK/PGC-1 α axis activation participated in the analgesic effect of Curcumin in SNI-induced neuropathic pain.

Despite above significant findings, our research focused exclusively on spinal cord mechanisms; whether supraspinal centers are also involved in curcumin's effects remains an open question. Our study design involved a relatively short-term treatment; the long-term efficacy and potential safety of chronic curcumin administration for neuropathic pain warrant future investigation. Subsequent studies could also explore the effects of curcumin on other spinal cord cell types, such as astrocytes, and investigate the potential synergistic effects of curcumin with existing analgesics.

In summary, this study indicates that the administration of Curcumin in mice alleviates the NP induced by SNI. Curcumin's protective effect may be associated with its capacity to inhibit microglia activation and modulate the AMPK/PGC-1 α pathway. These results highlight the potential therapeutic use of Curcumin in the development of novel analgesic drugs.

Conclusions

In conclusion, this study demonstrates that curcumin alleviates SNI-induced neuropathic pain by regulating spinal AMPK/PGC-1 α signaling and inhibiting microglia activation. Our findings establish curcumin as a promising therapeutic candidate for managing neuropathic pain.

Declarations

Date Availability

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

Conflicts of Interest:

The authors declare no conflicts of interest.

Ethics and Consent to Participate declarations:

All animal experiments were approved by the Animal Ethics Committee of Hubei No. 3 People's Hospital. Consent to participate is not applicable as no human subjects were involved.

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Author Contribution

Qian Zhou: Conceptualization, Data curation, Formal analysis, Methodology. Xin Li: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. Wang Li: Data curation, Formal analysis, Investigation. Kai Song: Investigation, Methodology. Xiaojun Zhou: Investigation, Methodology. Qihao Yang: Investigation, Methodology. Xue Bai: Conceptualization, Resources, Supervision, Validation. Chenghong Sun: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing. All authors read and approved the final manuscript.

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Figures

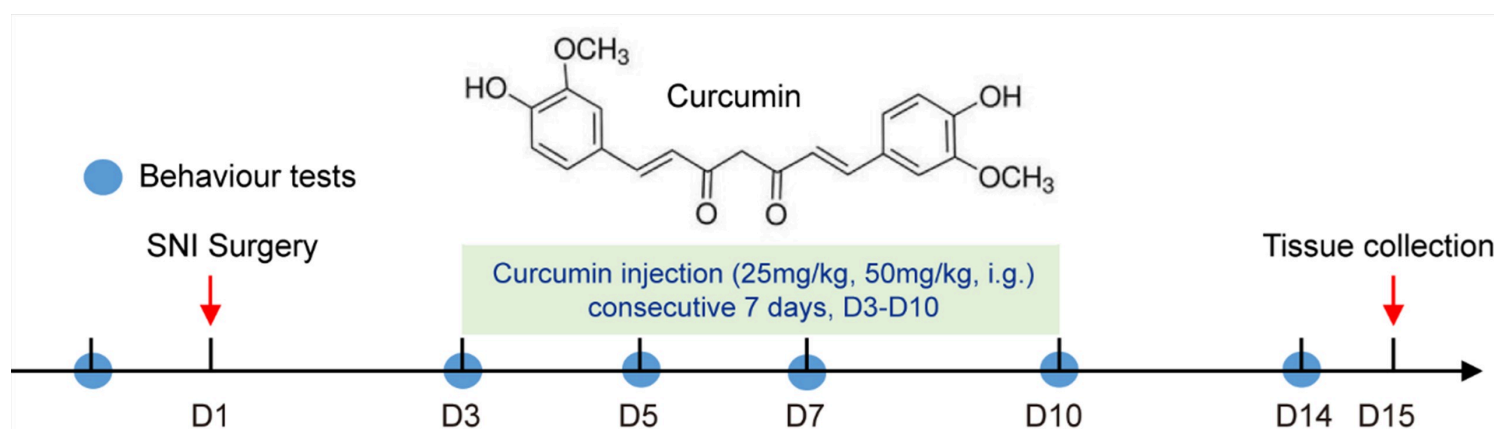


Figure 1

Chemical structure of curcumin and protocols of this study.

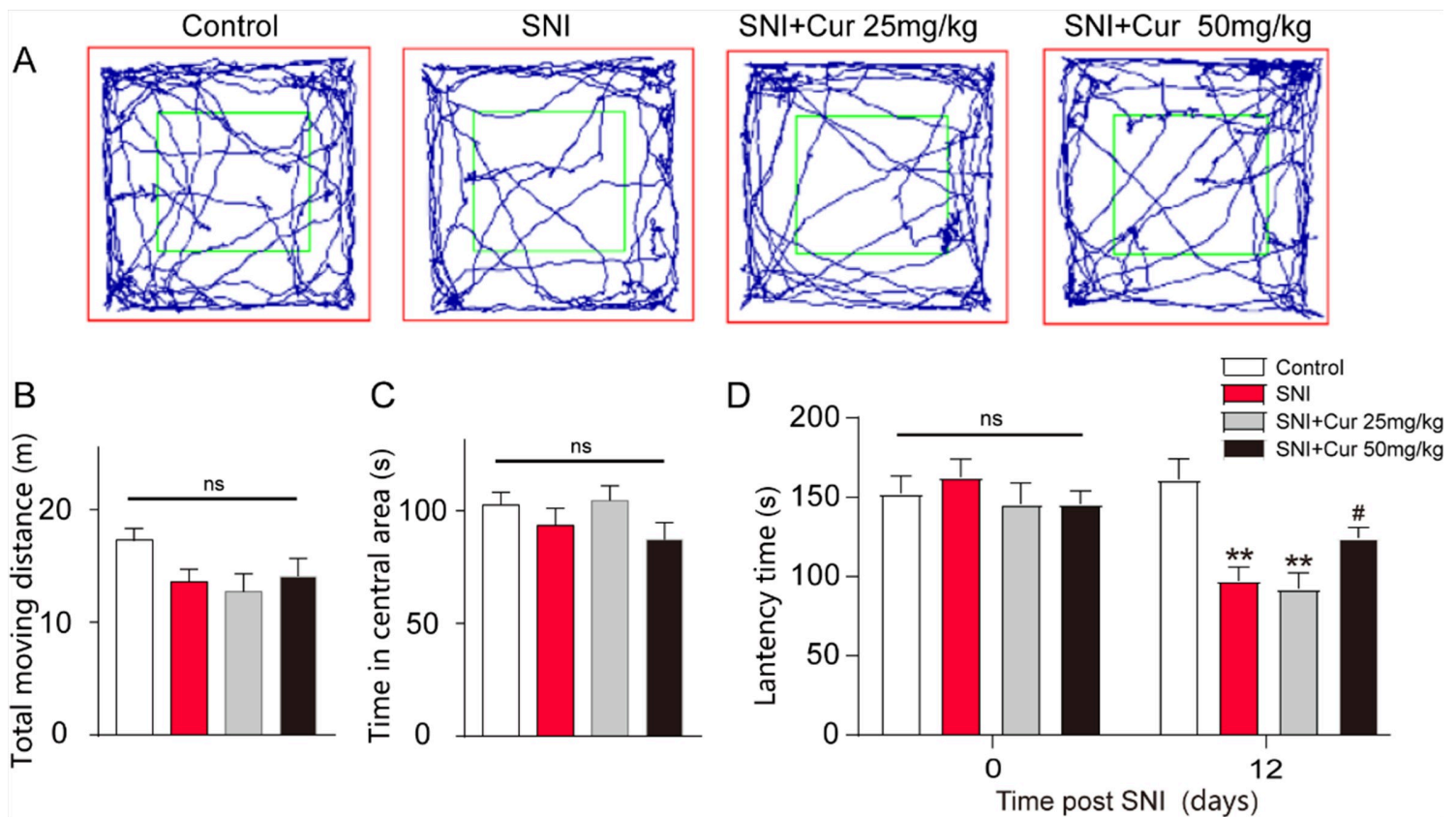


Figure 2

Effects of consecutive administration of curcumin on locomotor activity in mice.

(A) Representative track map of mice in the open field test. (B) The total moving distance of mice in the open field test on day 12. (C) The duration time spent in the center area of mice in the open field test on day 12. (D) The latency to fall in the rotarod test on day 12. ** $P < 0.01$ vs. control group; # $P < 0.05$ vs. SNI group. (n = 8 mice/group).

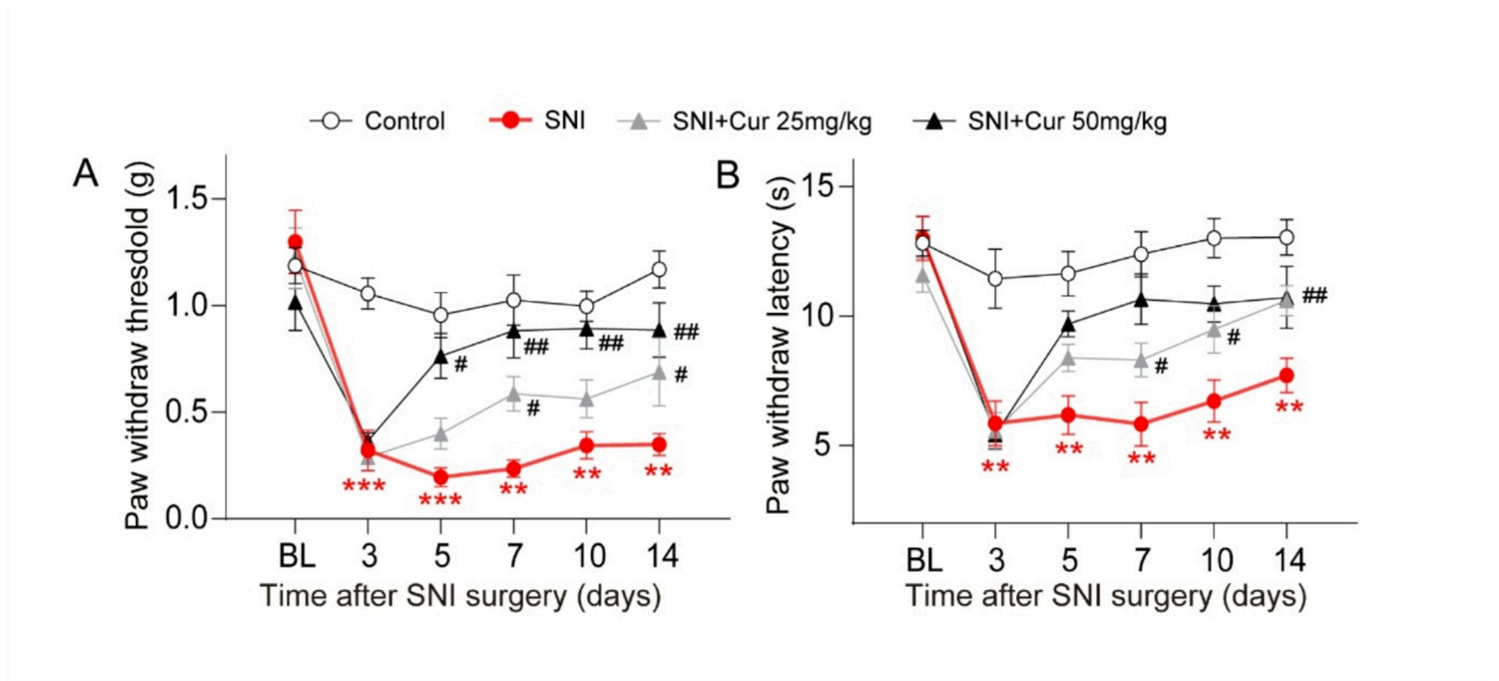


Figure 3

The analgesic effects of curcumin on SNI-induced neuropathic pain in mice over time.

(A) Effect of curcumin on PWT of mice in Von Frey test on day 3, 5, 7, 10, and 14. (B) Effect of curcumin on PWL of mice in hot-plate test on day 3, 5, 7, 10, and 14. ** $P < 0.01$, *** $P < 0.001$, vs. control group; # $P < 0.05$, ## $P < 0.01$ vs. SNI group. (n = 8 mice/group).

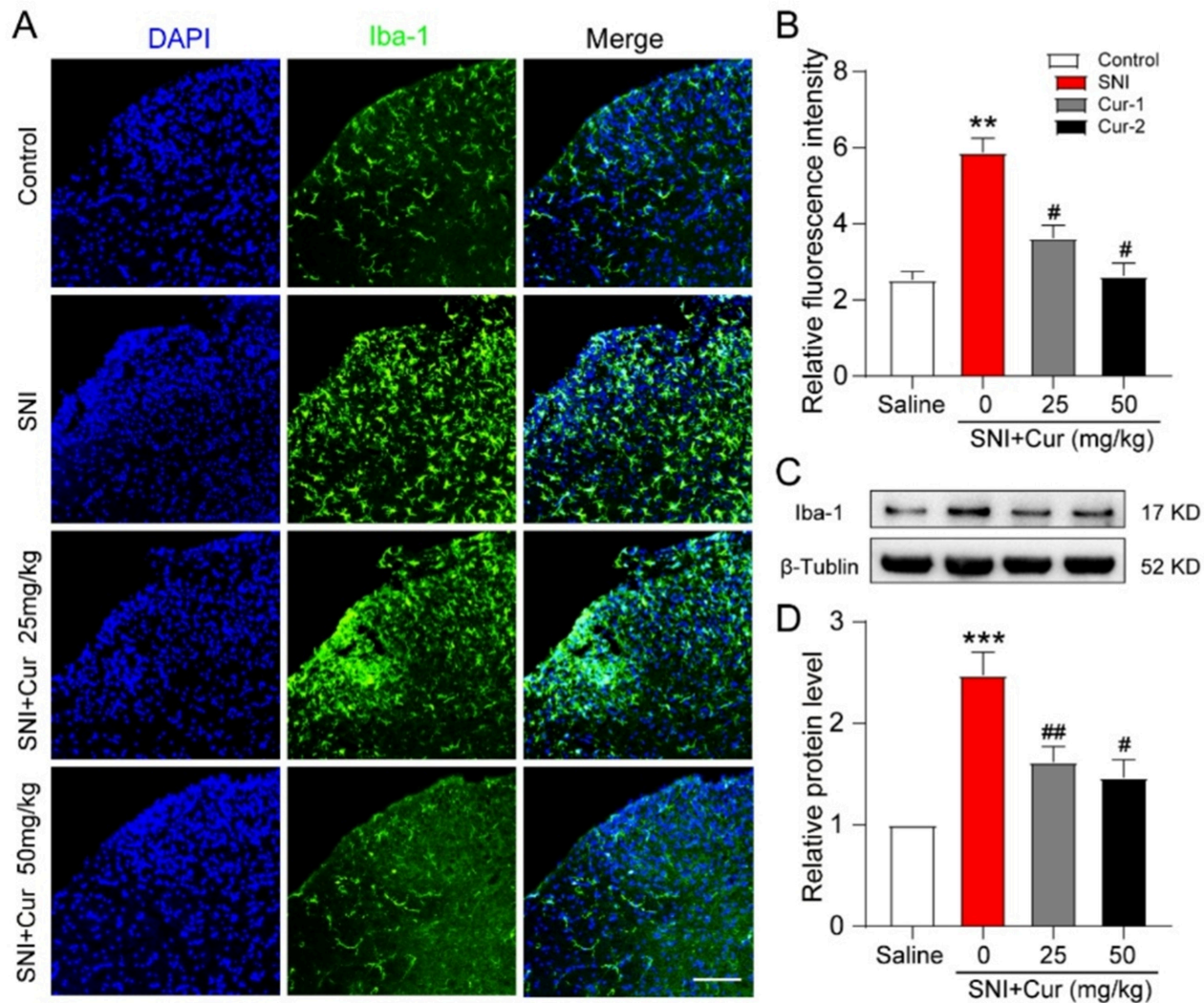


Figure 4

Effect of repeated Curcumin on the expression of microglial activation marker Iba-1 in lumbar L4-L6 spinal cord of mice.

(A) Immunostaining for Iba-1 in spinal cord segments from mice among all groups. Scale bar = 100 μ m, (B) Quantification of fluorescence intensity for Iba-1 in spinal cord segments from mice among all groups. (C-D) Western blot and quantification of Iba-1 protein of each group mice in spinal cord. ** $P < 0.01$, *** $P < 0.001$ vs. control group; # $P < 0.05$, ## $P < 0.01$ vs. SNI group. (n = 5 mice/group).

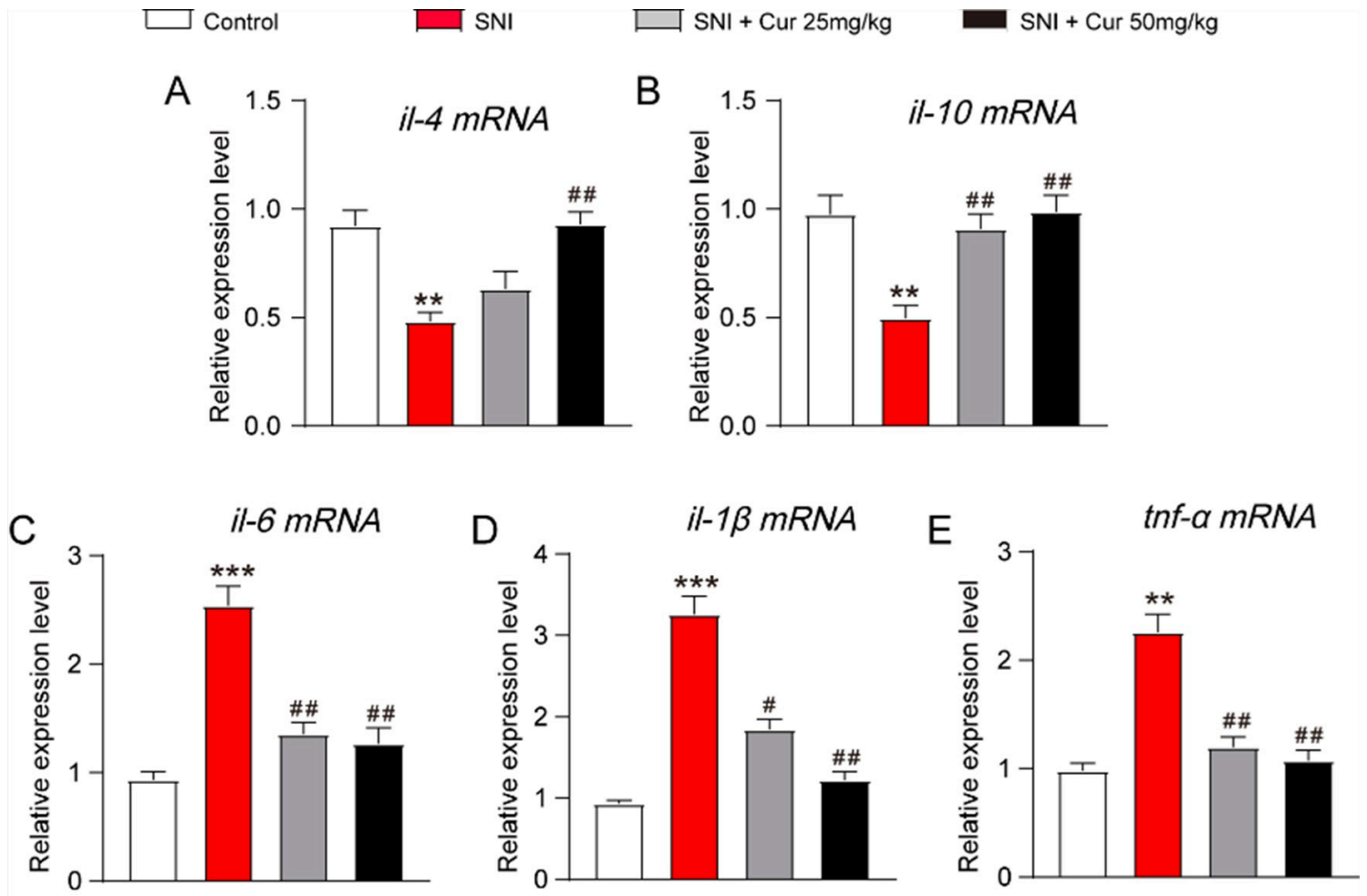


Figure 5

Effect of repeated curcumin administration on spinal expression of inflammatory cytokines in SNI mice.

(A-B) The mRNA levels of anti-inflammatory cytokines Il-4 and Il-10 in the L4-L6 spinal cord were measured by qRT-PCR. (C-E) The mRNA levels of pro-inflammatory cytokines Il-6, Il-1 β and Tnf- α in the L4-L6 spinal cord were measured by qRT-PCR. Data are presented as mean $\pm$ SEM. ** P < 0.01, *** P < 0.001 vs. control group; # P < 0.05, ## P < 0.01 vs. SNI group. (n = 5 mice/group).

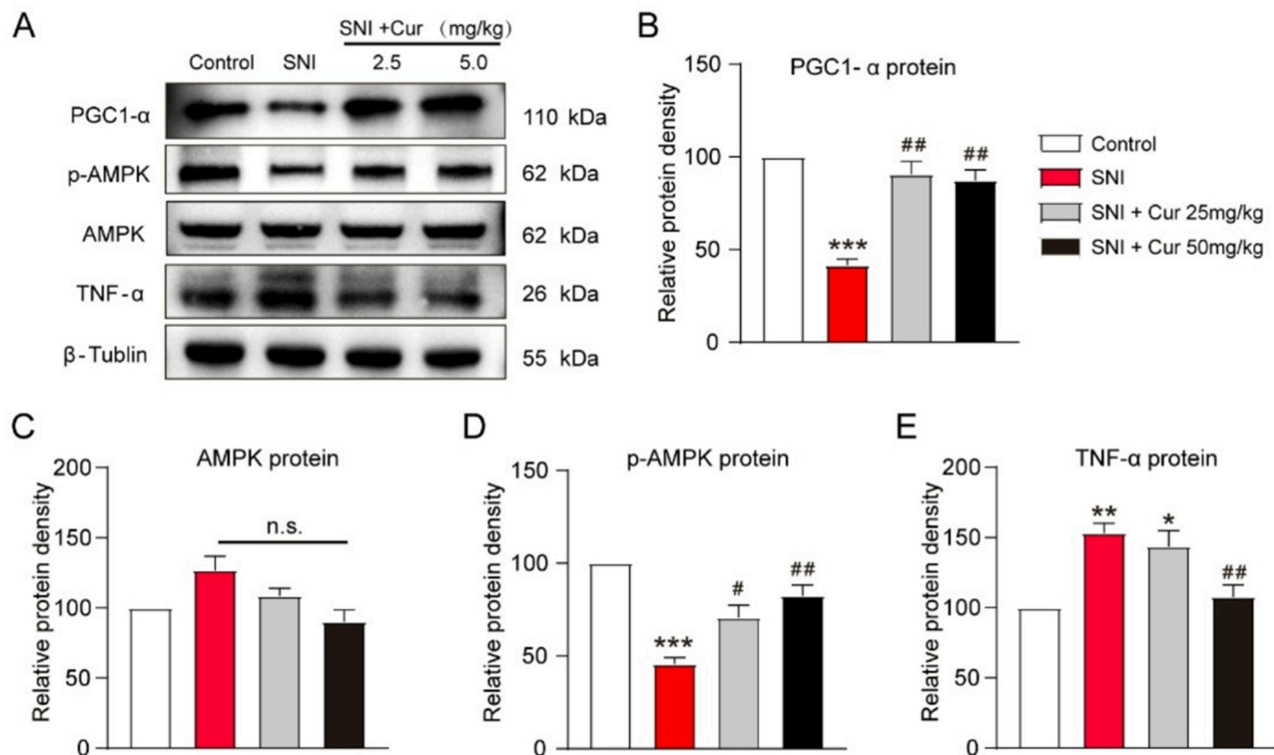


Figure 6

Curcumin reversed the up-regulation of p-AMPK, PGC-1α and TNF-α in spinal cord of mice.

(A) Western blot of AMPK/p-AMPK, PGC-1α and TNF-α protein. (B-E) Quantification of AMPK/p-AMPK, PGC-1α and TNF-α protein from mice among all groups. Data are expressed as mean ± SEM. * $P < 0.05$, ** $P < 0.01$ vs. control group; # $P < 0.05$, ## $P < 0.01$ vs. SNI group. (n = 5 mice/group).

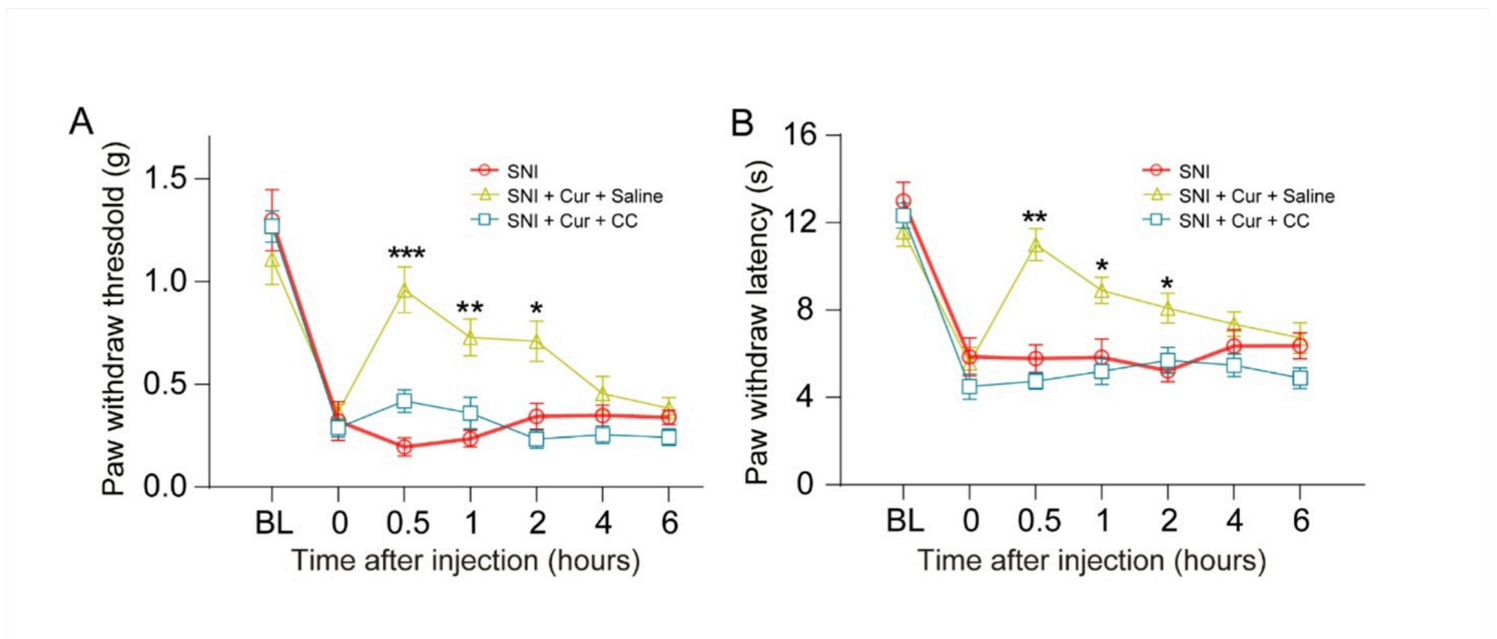


Figure 7

Effects of AMPK inhibitor Compound C on pain behavior in mice.

(A) Effect of Compound C on PWT of mice in Von Frey test at 0, 0.5, 1, 2, 4 and 6 hours after administration. (B) Effect of Compound C on PWL of mice in hot-plate test at 0, 0.5, 1, 2, 4 and 6 hours after administration. ** $P < 0.05$, * $P < 0.01$, *** $P < 0.001$, vs. control group. (n = 8 mice/group).

Supplementary Files

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- [WBpAMPK.png](#)
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- [WBAMPK.png](#)
- [WBPGC1.png](#)
- [WBTNF.png](#)