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ORIGINAL RESEARCH

Curcumin Alleviates Chronic Pain and Improves Cognitive Impairment via Enhancing Hippocampal Neurogenesis in Sciatic Nerve Constriction Rats

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Purpose: Cognitive impairment is a complication that most frequently happens in patients with chronic neuropathic pain and has limited effective therapy. The aim of this study was to explore the effects of curcumin on the cognitive deficit in rats with peripheral nerve injury induced-neuropathic pain.

Methods: The neuropathic pain rat model was constructed using chronic constriction injury (CCI). The curcumin (60 mg/kg) or vehicle was intraperitoneally administered once a day, beginning at 14th day after surgery and continued for 14 consecutive days. The nociceptive threshold tests were measured by paw mechanical withdraw threshold (PMWT) and paw thermal withdrawal latency (PTWL), while the spatial memory abilities were evaluated by the Morris water maze test. The mean counts of bromodeoxyuridine (Brdu)/neuronal nuclei (NeuN) as well as Brdu/doublecortin (DCX) co-labeled cells were used to evaluate neurogenesis in the dentate gyrus of hippocampus. The ultrastructure of the synapse in hippocampal region was visualized using transmission electron microscopy (TEM).

Results: Increased PMWT and PTWL, as well as relieved memory deficits, were found in CCI rats under curcumin administration. Moreover, curcumin treatment increased the number of newly born immature (BrdU/NeuN) and newly generated mature neurons (BrdU/DCX). The TEM examination revealed increased PSD thickness and shorter active zone length as well as narrowed synaptic cleft width in the hippocampal region of CCI rats after curcumin injection.

Conclusion: Curcumin can alleviate CCI induced nociceptive behaviors and memory deficit. This effect might be associated with hippocampal neurogenesis and synaptic plasticity improvements, which indicated curcumin as a potential strategy for the cognitive impairment restoration under prolonged neuropathic pain condition.

Keywords: curcumin, peripheral nerve injury, cognitive impairment, hippocampus neurogenesis

Introduction

Patients with chronic pain frequently experienced cognitive impairment commonly characterized as memory and learning capacity deterioration, which deteriorates the quality of life and even increases patients' financial burdens.[1] Numerous evidences have revealed that memory deficits in patients with chronic pain could be attributed to the severity of the patients' emotional disturbances, including anxiety and depression.[2,3] Previous studies report the mean prevalence rates of around 20–30% for cognitive function impairment in patients with chronic neuropathic

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pain.[4,5] Preclinical researches revealed that the neuropathic pain-related behaviors usually accompany with spatial learning as well as memory disorders in murine models with chronic peripheral nerve injury.[6,7] However, although the link between chronic pain and the development of cognitive dysfunction has been extensively studied and documented, limited therapeutic options are available up to now, indicating that the molecular aspects underlying chronic pain-associated learning and memory deficits have not been well understood.

The hippocampus, a crucial component of the limbic system, is considered to play an important role during memory and mood formation in brain. Recent preclinical evidences have showed that chronic peripheral nerve injury exposure could decrease neurogenesis process in the dentate gyrus (DG) granular cell layer of adult hippocampus.[1,8] The deficits in hippocampal neurogenesis might decline the generation of new immature neurons in hippocampus that promote the clearance of panic memory and maintain the ability of animal to cope with environmental challengers,[9] while restoring the impaired hippocampal neurogenesis in chronic neuropathic or inflammatory pain models were beneficial for alleviation of painful syndromes.[10] Additionally, it is noteworthy that the animals with a reversible neuropathic injury might persistently display cognitive impairment behaviors accompanied with constant ablation of hippocampal neurogenesis, indicating even after recovery from the physical pain of the neuropathy, its more long-term stressing consequences endure on the nervous system, and that impaired neurogenesis might be involved in the emergence of these consequences.[11] Thus, enhancing the blocked hippocampal neurogenesis after peripheral nerve injury might be a key to improve cognitive function during chronic pain.

Curcumin, a phenolic compound derived from the rhizome of Curcuma longa, has been widely studied for its analgesic properties against various neuropathic pains.[12–15] Recently, curcumin was demonstrated to be able to improve pain behaviors as well as cognitive impairments in cobra venom-induced trigeminal neuralgia and chronic constriction injury (CCI) rodents, which suggested the benefit effects of curcumin on neuroprotective property and improvement of learning and memory performances in chronic neuropathic pain models.[7,16] However, it remains unclear whether curcumin treatment can increase hippocampal neurogenesis and improve cognitive dysfunctions in neuropathic pain elicited by peripheral nerve injury. This study was designed to report a causal evidence that curcumin plays a potential role in improving cognitive function in chronic constriction injury (CCI) pain model owing to its hippocampal neurogenesis-promoting property.

Methods

Study Approval and Animal Preparation

All protocols of the current study were approved by the Animal Ethical Committee of the Third Affiliated Hospital, Sun Yat-Sen University, and conducted in accordance with the guidelines of the International Association for the Study of Pain.

Male Sprague Dawley rats (200–250 g) were obtained from the Experiment Animal Center of Guangdong Province (SCXK [Yue] 20180002) and maintained in separate cages under a 12-h light/dark cycle, with water and fed available ad libitum. The room was kept at temperature (23 ± 2°C) as well as humidity (50–60%). We made all efforts to minimize the number of animals used and their suffering.

Procedures of Pain Model Establishment

Anesthesia was administrated by intraperitoneal injection of pentobarbital sodium (50 mg/kg). Then, rats were performed either a unilateral CCI or a sham procedure as depicted by Bennett et al.[17] In short, the CCI model was established by a ligation at the left sciatic nerve using four ligatures with non-absorbable 4/0 silk threads (1.0- to 1.5-mm spacing between each ligature), while only exposure of the left sciatic nerve without ligation was performed on sham rats.

Drug Treatments

By a random table, 40 rats were randomly divided into four groups, as follows (i) sham with curcumin group (Sham + Cur, n = 10); (ii) CCI with curcumin group (CCI + Cur, n = 10), (iii) sham with vehicle group (Sham + Veh, n = 10), or (iv) CCI with vehicle group (CCI + Veh, n = 10). According to the study from Zhu et al,[11] curcumin (Sigma-Aldrich, Santa Clara, CA, USA) was dissolved in 20% dimethyl sulfoxide (DMSO) with 80% normal saline solution. The curcumin (60 mg/kg) or vehicle (20% DMSO with 80% normal saline solution) was intraperitoneally administered once a day, which start at 14th day after surgery and continued for 14 consecutive days (Figure 1).

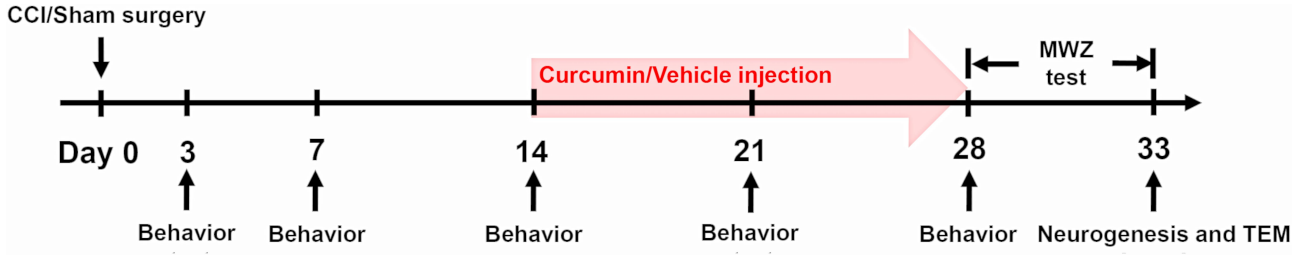

Figure 1 Timeline of CCI or sham surgery, curcumin or vehicle (20% DMSO with 80% normal saline solution) injection, behavior and MWZ tests, neurogenesis and TEM detection.
Abbreviations: CCI, chronic constriction injury; DMSO, dimethyl sulfoxide; MWZ, Morris water maze; TEM, transmission electron microscopy.

Mechanical and Thermal Nociceptive Threshold Test

In order to determine whether the CCI model was well established, both paw mechanical withdraw threshold (PMWT) and paw thermal withdrawal latency (PTWL) were assessed 3 days before surgery and 3, 7, 14, 21 and 28 days by two research staffs who were blinded to the group (Figure 1). The behavior test was performed in a noise-free room. Each rat was placed individually on a wire mesh grid (mechanical nociceptive threshold test) or glass floored box (thermal nociceptive threshold test). At least 30 min was allowed to habituate to the surroundings.

The PMWT was assessed by the von Frey monofilaments (North Coast Medical, California, USA) weighing 1.0–15.0 g. The ascending series monofilaments were used to perpendicularly stimulate the mid-plantar surface of hind paw, and each was presented five times with an interval of 4–6 s. A positive response was considered a withdrawal, along with shaking or licking of the paw at least three times over the course of five applications. The smallest bending force of the monofilament eliciting a positive response was determined to be the PMWT.

The PTWL was measured through the thermal test apparatus (UGO BASILE 37370 Plantar Test Apparatus, Italy), which could release a focused radiant heat source from below the glass onto the mid-plantar surface of the hind paw. According to Dai et al,[18] the infrared intensity was set as 45 with a cutoff time of 25 s to avoid cutaneous damage to the hind paw. This thermal nociceptive threshold test was repeated five times, and the PTWL was considered as the mean latency of withdrawal response across five tests.

Morris Water Maze Test

When the curcumin had been administrated for 14 consecutive days, a five-day Morris water maze (MWZ) test was applied to evaluate the spatial memory abilities, according to previous study[19] (Figure 1). Briefly, a circular pool (180 cm diameter and 60 cm high), which was full of 19°C to 22°C opaque water and divided into four equivalent quadrants (N, E, S, and W), was prepared for the MWZ test. A hidden escape platform was placed in one of four quadrants and submerged 0.5 cm below the water. For the first four days, rodents underwent four acquisition trials separated by 20-minute inter-trial interval per day. During the four acquisition trials, rats were placed into the water facing the pool at different predetermined positions. The swimming speed and escape latency were recorded. On fifth day, the hidden escape platform was removed, and rats were placed into the pool at the location opposite to the platform position and allowed to swim freely for 120 s. According to the previous study,[20] we recorded the percentage time spent in the target quadrant and times across platform. Moreover, the time spent in the platform quadrant and the remaining three quadrants were respectively recorded for each group. Whole MWZ test was performed by two research staffs who were blinded to group allocation.

BrdU Administration

To examine the effects of curcumin on neural precursor cells proliferation in the DG of the hippocampus, rats received intraperitoneal injection of 100 mg/kg bromodeoxyuridine (BrdU) (Sigma-Aldrich, B5002) once a week studying from the day receiving CCI or sham surgery until sacrifice, which was according to the previous study.[10] Two hours after the last BrdU injection, rats were anesthetized and hippocampus tissues were prepared for the following immunofluorescent and transmission electron microscopy.

Immunofluorescent

The hippocampus tissues were separated after MWZ test (Figure 1) and post-fixed at 4°C overnight, followed by the dip in a 30% sucrose solution for 48 h. Sections of 30 μm thick were prepared by a freezing microtome (VT1000S, Leica Microsystems). For all cases, slices were incubated with the mouse anti-doublecortin (DCX, 1:500, ab254133, Abcam), rabbit anti-BrdU (1:200, ab152095, Abcam), mouse anti-neuronal nuclei (NeuN, 1:400, ab104224, Abcam) antibodies. The secondary antibodies were tagged with goat anti-mouse Alexa 594 (1:500, ab150120, Abcam), goat anti-rabbit Alexa 488 (1:500, ab150081, Abcam). Then slices were stained with 4′,6-diamidino-2-phenylindole (DAPI, 0.5μg/mL, 4083s, Cell Signaling Technology). After staining, slices were visualized by two experimenters blinded to group allocation with the laser scanning confocal microscopy (FV1000; Olympus). The mean counts of Brdu/NeuN as well as Brdu/DCX co-labeled cells in every fifth section for each animal was used to evaluate neurogenesis in the DG.

Transmission Electron Microscopy Examination

The collected hippocampus tissues from rats were perfused in 2% paraformaldehyde and 2% glutaraldehyde in 0.1 M sodium cacodylate, followed by post-fixation in 2% osmium tetroxide with 1.6% potassium ferrocyanide in 0.1 M sodium cacodylate. Subsequently, the hippocampus tissue samples were cut into small clumps of a volume of 1 mm^3 and dehydrated through a graded acetone series, after which they were embedded in Eponate 812 medium (90529–77-4, Structure Probe, Inc., Pennsylvania, USA). Finally, the sections were placed on copper slot grids and stained with 2% uranyl acetate and lead citrate. Images were visualized by Hitachi HT-7700 transmission electron microscopy (Tokyo, Japan). As previously described,[21,22] the morphologic features of synapse including postsynaptic dense (PSD) band, active zone and synaptic cleft were observed, and the mean values of thickness of the postsynaptic density, length of active zone as well as width of the synaptic cleft in every fifth DG region section was calculated.

Statistical Analysis

Data analysis and statistics were performed by SPSS 20.0 software (IBM CORP, New York, USA). Data were presented as mean ± standard deviation (SD), and analyzed by a two-way analysis of variance (ANOVA) with repeated measures followed by Bonferroni post hoc comparisons. Statistical significance was set as $P < 0.05$.

Results

Effect of Curcumin on Mechanical Allodynia and Thermal Hyperalgesia

In comparison to rats in the Sham + Cur and Sham +Veh groups, those in the CCI + Veh group exhibited significant reductions of the mechanical threshold ($P < 0.001$; Figure 2A) and thermal latency ($P < 0.001$; Figure 2B) after sciatic nerve injury, which were throughout the 28-day observation period. However, curcumin treatment markedly attenuated the mechanical allodynia ($P < 0.001$; Figure 2A) and thermal hyperalgesia ($P < 0.001$; Figure 2B) in rats from CCI +Cur group. These results suggested that consecutively administrating 60 mg/kg curcumin for 14 days might alleviate both mechanical and thermal hyperalgesia resulted from peripheral nerve injury.

Effect of Curcumin on Spatial Memory Function

Compared to the sham rats received vehicle, the significantly longer escape latency to platform ($P < 0.001$, Figure 3A) for CCI rats treated with vehicle indicated that the cognitive impairment was induced by peripheral nerve injury. While the administration of curcumin restored the increased escape latency resulted from CCI ($P < 0.001$, Figure 3A). However, we did not observe any significant differences in swimming speed among four groups (Figure 3B). The rats in CCI-Veh group presented significant shorter swimming time in target quadrant ($P < 0.001$, Figure 3C) and time across platform was reduced ($P < 0.001$, Figure 3C) than those for the rats from sham-Veh group; on the contrary, both parameters were significantly prolonged after the injection of curcumin ($P = 0.021$ for time in target quadrant, $P = 0.019$ for time across platform, Figure 3C and D). Besides, there was no significant difference in the spent time among four quadrants in CCI rats treated with vehicle, while the CCI rats treated with curcumin spent more time in the platform quadrant than other three quadrants ($P < 0.01$, Figure 4).

Effect of Curcumin on Hippocampal Neurogenesis in DG Region

Double labeling of proliferating neurons with anti-BrdU and other marker could provide indication for the phenotype of marked cells.[23] Thus, we counted the number of double

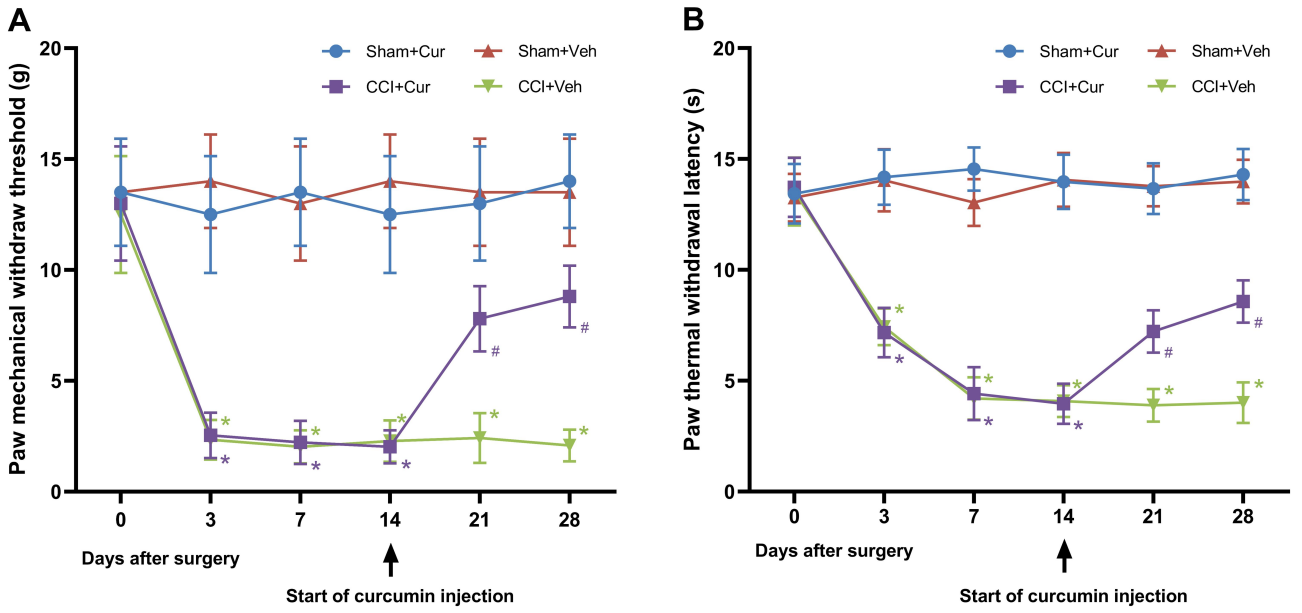

Figure 2 Time-course changes of mechanical threshold (**A**) and thermal latency (**B**) in the ipsilateral hind-paw of rats.
Note: *P < 0.001 vs Sham+Veh, #P < 0.001 vs CCI+Veh.
Abbreviations: CCI, chronic constriction injury; Veh, vehicle; Cur, curcumin.

immunostaining cells to identify newly born immature (BrdU/NeuN)[24] and newly generated mature neurons (BrdU/DCX),[23] respectively.

Four weeks after injury, the number of BrdU/NeuN (Figure 5) and BrdU/DCX (Figure 6) neurons was significantly lower in the dentate gyrus of the rats in CCI-Veh group compared to those in sham-Veh group Sham mice ($P = 0.041$ for BrdU/NeuN, $P < 0.001$ for BrdU/DCX). Notably, the number of BrdU/NeuN and BrdU/DCX double labeled neurons in the dentate gyrus was dramatically increased in the curcumin administered CCI rats ($P = 0.014$ for BrdU/NeuN, $P = 0.015$ for BrdU/DCX, Figures 5 and 6).

Effect of Curcumin on the Hippocampal DG Synapse Density

Compared with the Sham-Veh groups, a noticeably changed synapse density along with the lesser PSD thickness ($P = 0.002$), shorter active zone length ($P = 0.006$) and wider synaptic cleft width ($P = 0.001$) was found in the DG region of the CCI-Veh group (Figure 7). In contrast, when the CCI rats were treated with curcumin, the aforementioned abnormality of hippocampal synapse density in CCI-Veh rats appeared to return to be regular ($P = 0.036$ for PSD thickness, $P = 0.044$ for active zone length, $P = 0.038$ for synaptic cleft width), similar to the morphologic features of synapse in sham rats (Figure 7).

Discussion

Our current results make the argument that curcumin treatment alleviated pain and improved cognition deficits in a peripheral nerve injury-induced neuropathic pain rat model. Furthermore, the protective effect of curcumin against neuropathic pain-caused cognitive impairment is partly associated with improving hippocampal neurogenesis.

Various functional and morphological alterations that related to the spatial learning and memory function impairments had been studied in neuropathic pain murine models. For example, Saffarpour S et al found that the increase in GABA concentration and decrease in the glutamate and BDNF levels in the CA1 region of the hippocampus were associated with spatial learning and memory function disorders comorbid in CCI rats.[25] Our current study using the CCI model shows that a prolonged pain performance (28-day CCI) impairs spatial memory formation along with reductions in the numbers of newly born immature and newly generated mature neurons in hippocampal DG region, which were in accordance with prior studies.[1,10] It was demonstrated that newborn neurons in the DG region are incorporated into the hippocampal network in existence and contributed to new cellular and behavioral capacities.[26,27] Compared with their mature counterparts, newborn neurons in the DG region were appeared to be more involved in new experience-related learning capacity

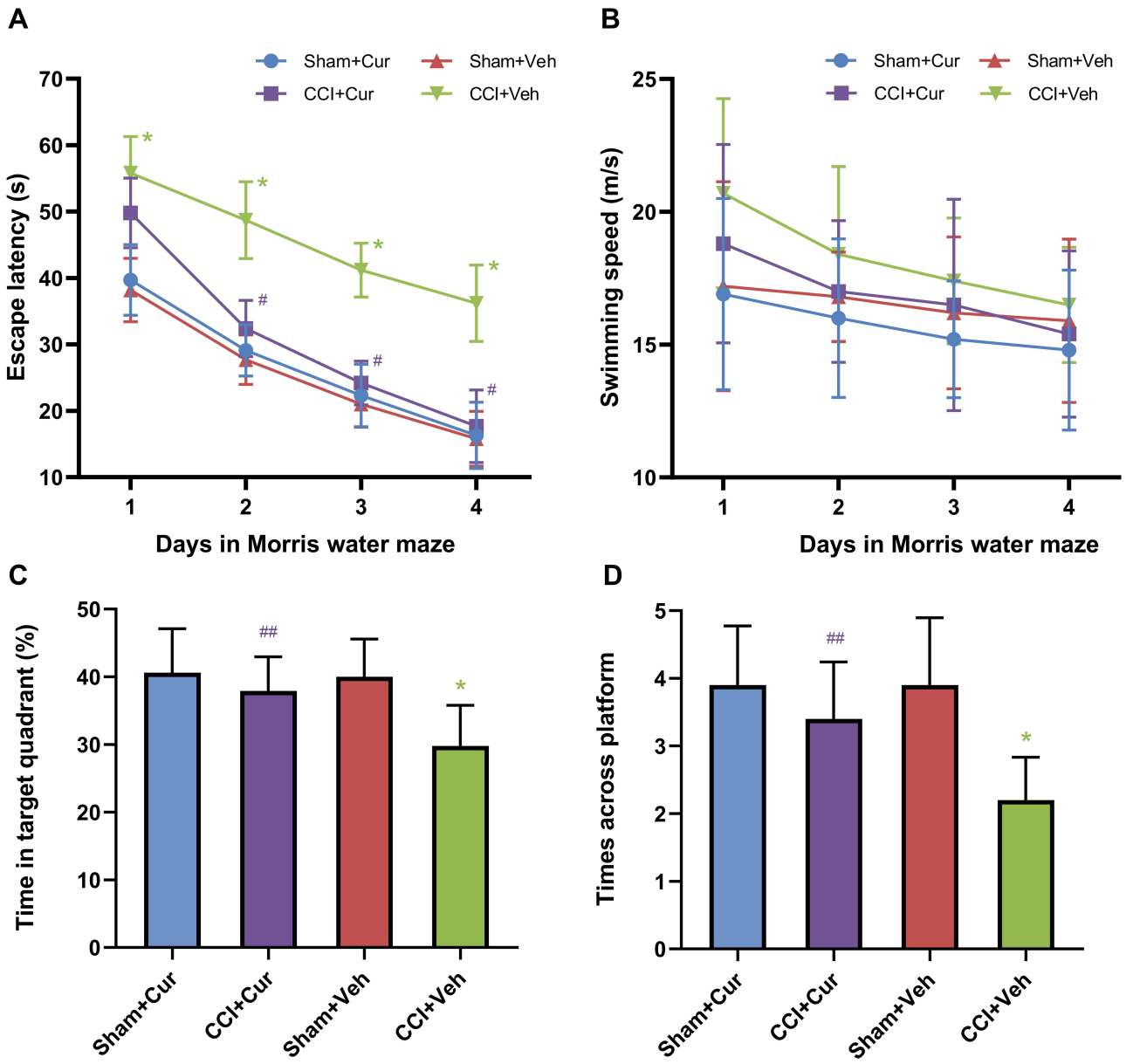

Figure 3 Time-course changes of escape latency (**A**), swimming speed (**B**), swimming time in target quadrant (**C**), time across platform (**D**) and spending times in four quadrants in the rats from different groups.
Note: *P < 0.001 vs Sham+Veh, #P < 0.001 vs CCI+Veh, ## P < 0.05 vs CCI+Veh.
Abbreviations: CCI, chronic constriction injury; Veh, vehicle; Cur, curcumin.

and memory formation.[28] More specifically, mice received mitotic inhibitor displayed increased escape latency and decreased time spent in the target quadrant, accompanied by a reduced number of newborn neurons in the DG region.[1] These results confirm that disruption of hippocampal neurogenesis may at least in part act as a trigger to spatial memory impairment during the development of neuropathic pain.

Considering the connection between hippocampal neurogenesis and memory formation, it was hypothesized that facilitating hippocampal neurogenesis would be helpful to improve integration of newborn neurons into hippocampal networks and alleviate pain-induced spatial memory impairment. Our results revealed that repeated administration of 60-mg/kg curcumin was able to relieve spatial memory impairment as well as nociceptive behavior in CCI rats, which were in concert with the previous studies.[12–16] More specifically, such effects of curcumin on cognitive impairments were appeared to be associated with improvement of hippocampal neurogenesis in CCI rats. The earlier findings

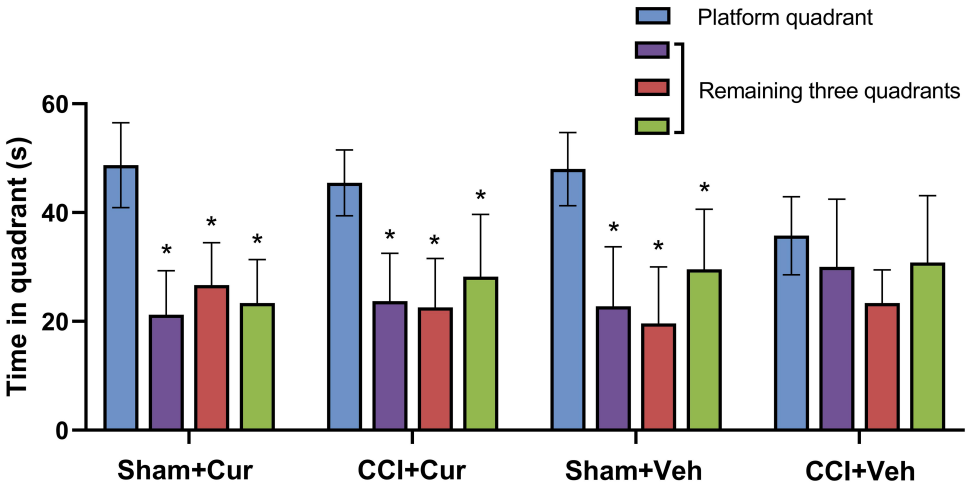

Figure 4 Time spent in four quadrants in the rats from different groups.
Note: *P < 0.001 vs time spent in platform quadrant.
Abbreviations: CCI, chronic constriction injury; Veh, vehicle; Cur, curcumin.

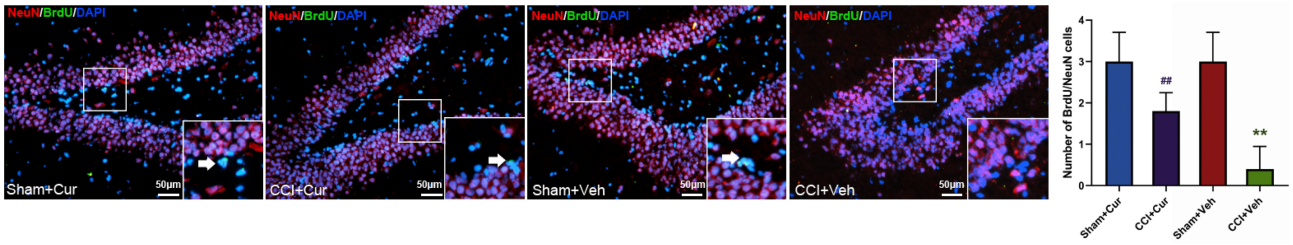

Figure 5 Representative images and quantitative summary of hippocampal NeuN/BrdU cells in the DG regions from rats in different groups (The white arrows represent NeuN/BrdU double labeled neurons).
Note: **P < 0.05 vs Sham+Veh, ## P < 0.05 vs CCI+Veh.
Abbreviations: CCI, chronic constriction injury; Veh, vehicle; Cur, curcumin; BrdU, bromodeoxyuridine; NeuN, neuronal nuclei; DAPI, 4′,6-diamidino-2-phenylindole; DG, dentate gyrus.

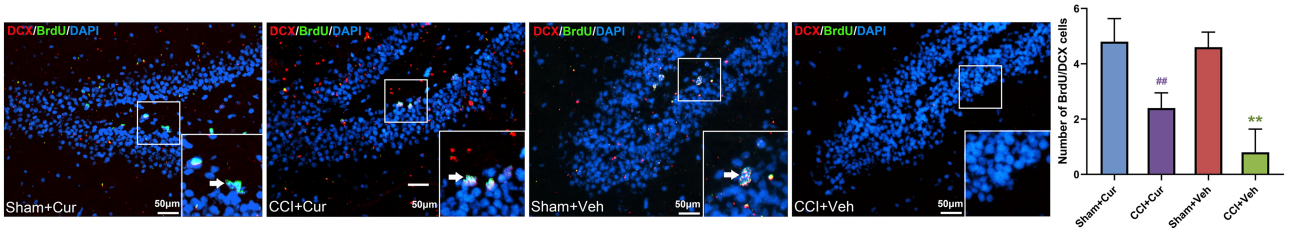

Figure 6 Representative images and quantitative summary of hippocampal DCX/BrdU cells in the DG region from rats in different groups (The white arrows represent DCX/BrdU double labeled neurons).
Note: **P < 0.05 vs Sham+Veh, ## P < 0.05 vs CCI+Veh.
Abbreviations: CCI, chronic constriction injury; Veh, vehicle; Cur, curcumin; BrdU, bromodeoxyuridine; DCX, doublecortin; DAPI, 4′,6-diamidino-2-phenylindole; DG, dentate gyrus.

had reported that the enhancement effects of curcumin on hippocampal neurogenesis might attribute to the activation of the Extracellular Signal Regulated Kinase (ERK) and Mitogen Activated Protein (MAP) kinase pathways.[29] More recently, the promotion effect of curcumin treatment on neurogenesis and memory was found to be via activation of adenosine monophosphate-activated protein kinase (AMPK)/c-Jun N-terminal kinase (JNK) signaling, which mediated both mammalian target of rapamycin (mTOR) inhibition and B-cell lymphoma-2 (Bcl-2) upregulation and in turn respectively enhanced autophagy and suppressed apoptosis in hippocampus.[30,31]

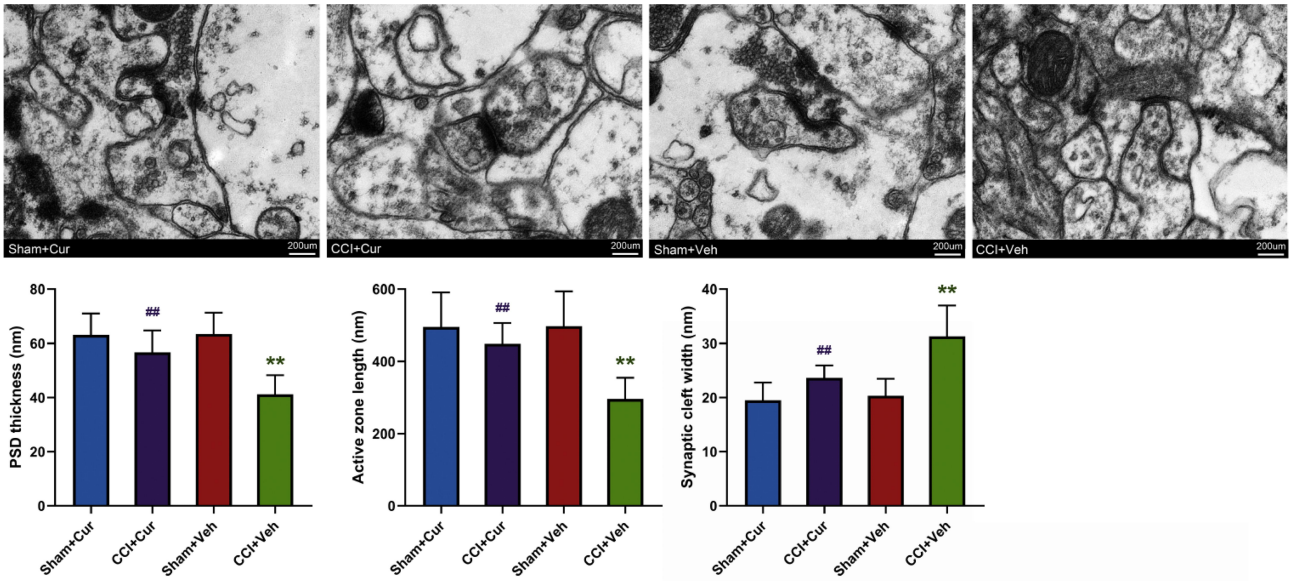

Figure 7 Representative images and quantitative summary of synaptic ultrastructure in the hippocampal DG region as visualized by TEM.
Note: **P < 0.05 vs Sham+Veh, ## P < 0.05 vs CCI+Veh.
Abbreviations: CCI, chronic constriction injury; Veh, vehicle; Cur, curcumin; PSD, postsynaptic dense; DG, dentate gyrus; TEM, transmission electron microscopy.

More importantly, production of new neurons in the hippocampus alone does not represent the complete process of neurogenesis, because the newly generated neurons must experience differentiation, maturation and then involve in formation of synapses.[32] In this study, the curcumin-treatment increased not only newly born immature (BrdU/NeuN) cell number but also newly generated mature neurons (BrdU/DCX) number, simultaneously. Moreover, the PSD thickness and shorter active zone length in parallel with narrow of synaptic cleft width returned to be regular in hippocampus tissue of CCI rats along with curcumin administration. Consequently, these current results indicated the possible involvement of neuronal and synaptic plasticities in the beneficial effect of curcumin on neuropathic pain-induced cognitive impairment.

Besides pro-neurogenic effect, the anti-inflammatory and anti-oxidant effects of curcumin on neuropathic pain had also been demonstrated by previous studies. It was reported that the administration of curcumin can ameliorate pain-related behavior and downregulate the production of pro-inflammatory cytokines, such as IL-1β, partly by inhibiting the aggregation of NALP1 inflammasome and the activation of the JAK2-STAT3 cascade in astrocytes.[33] In the oxaliplatin-induced peripheral neuropathic pain and diabetic neuropathy, curcumin could not only inhibit the activation of NF-κB and inflammatory factors, but inhibiting the level of oxidative stress as well.[33,34] These potential issues of curcumin effects on neuropathic pain warrant further experiments in further research.

Conclusion

In conclusion, our findings suggest that consecutively administrating 60 mg/kg curcumin for 14 days alleviates CCI induced nociceptive behaviors and memory deficit. This effect may be associated with hippocampal neurogenesis and synaptic plasticity improvements. Thus, we infer that curcumin would serve as a potential strategy for the cognitive impairment restoration under prolonged neuropathic pain condition. However, further clinical studies will be performed to clarify this possibility.

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Disclosure

The authors report no conflicts of interest in this work.

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