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Original Article

Electroacupuncture alleviates Parkinson's disease by inhibiting the NLRP3 inflammasome pathway

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Abstract: Objectives: To explore the therapeutic effects and potential mechanism of electroacupuncture (EA) in a Parkinson's disease (PD) mouse model. Methods: C57BL/6 mice were randomly assigned to control, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), MPTP + sham EA, and MPTP + EA groups. PD was induced by MPTP. EA was applied at Baihui (GV20), Hegu (LI4), and Taichong (LR3). After 20 days of treatment, behavioral tests including the open field test, rotarod test, and Morris water maze were conducted. Dopaminergic neuron survival, apoptosis, and expression of inflammatory markers were assessed. Results: MPTP-induced mice exhibited impaired motor and cognitive performance, increased brain apoptosis, reduced dopaminergic neurons, and elevated expression of α-synuclein, NLRP3, IL-1β, IL-18, caspase-1, and gasdermin D. These changes were not significantly altered by sham EA. In contrast, EA significantly improved motor and cognitive function, reduced apoptosis, preserved dopaminergic neurons, increased tyrosine hydroxylase expression, and suppressed NLRP3 inflammasome activation. Conclusion: EA mitigates PD symptoms and exerts neuroprotective effects by inhibiting NLRP3 inflammasome-mediated neuroinflammation.

Keywords: Electroacupuncture, inflammasome, NLRP3, Parkinson's disease, animal model

Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder affecting 2%-3% of individuals over the age of 65 [1, 2]. Its prevalence is projected to double over the next 30 years [3, 4]. PD results from a combination of environmental and genetic factors and is pathologically characterized by the degeneration of the substantia nigra and accumulation of α-synuclein (α-syn) in Lewy bodies [5]. Although current treatments offer symptomatic relief, they remain insufficient to halt disease progression, and no curative therapy exists to date [6, 7].

Acupuncture, a traditional therapy practiced in Asia for over 3,000 years [8], is based on stimulation of 365 specific points along 12 primary meridians, believed to regulate "qi and blood" [9]. Clinical and preclinical studies suggest that both manual and electroacupuncture (EA) can alleviate motor symptoms and significantly improve non-motor manifestations such as mood disturbances, gastrointestinal dysfunction, and sleep disorders in PD patients [10]. Mechanistically, acupuncture may exert neuroprotective effects via anti-inflammatory, antioxidant, and anti-apoptotic pathways, as well as by modulating neurotransmitter balance in the basal ganglia circuitry [11]. However, the molecular mechanisms underlying these effects remain poorly understood.

Inflammasomes, particularly NOD-like receptor family pyrin domain-containing proteins NLRP1 and NLRP3, are cytoplasmic multiprotein complexes involved in innate immunity [12]. The NLRP3 inflammasome typically includes NLRP3, ASC, and pro-caspase-1, and its activation leads to caspase-1-dependent maturation of interleukin (IL)-1β and pyroptotic cell death [13,

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14]. Inhibiting NLRP3-mediated neuroinflammation has been shown to slow PD progression, highlighting a promising therapeutic target [15]. Recent findings by Xin et al. indicate that EA attenuates neuroinflammation via multiple signaling pathways [16]. However, its specific role in modulating the NLRP3 inflammasome in PD remains unclear.

Given this background, EA, a modern adaptation of traditional acupuncture offering improved reproducibility and precision [17], may influence NLRP3 inflammasome activity. This study aimed to investigate the effects and underlying mechanisms of EA in a PD mouse model, with the goal of identifying novel therapeutic strategies and molecular targets for clinical intervention.

Materials and methods

Animals

Male C57BL/6 mice (21-25 g) were housed in a controlled environment (24 ± 2°C, 55% ± 5% humidity) under a 12 h light/dark cycle, with free access to food and water. PD was induced by intraperitoneal injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) at 20 mg/kg/day for 14 consecutive days [18]. Mice were randomly divided into four groups (n = 6 per group): control, MPTP model, MPTP + sham EA, and MPTP + EA. Control mice received saline injections. EA was administered at Baihui (GV20), Hegu (LI4), and Taichong (LR3) for 30 minutes daily over 20 days. Acupoint locations, depth, and stimulation parameters followed previously published protocols [19, 20]. In the sham group, needles were taped to the skin surface at the same acupoints without electrical stimulation. Behavioral tests were conducted after 20 days of treatment [21].

All animal procedures were approved by the Institutional Animal Care and Use Committee of Sun Yat-sen University (Approval No. SYSU-IACUC-2020-000224) and were conducted in compliance with the NIH Guide for the Care and Use of Laboratory Animals and ARRIVE guidelines. Mice were anesthetized during modeling to minimize pain and euthanized via cervical dislocation at the end of the experiment.

Open field test (OFT)

After 20 days of treatment, mice were placed individually into a white opaque open-field box and allowed to explore for 5 minutes. Behavioral parameters including time spent in the center and distance traveled, were recorded.

Rotarod test

The rotarod test was conducted to assess motor coordination [22]. Mice underwent one acclimation trial followed by three test trials. The rotating rod accelerated from 2 to 50 rpm over 5 minutes. Each trial lasted up to 5 minutes, with 30-minute intervals between trials. The average latency to fall in the last three trials was used for analysis.

Morris water maze (MWM)

Cognitive function was evaluated using the MWM [23, 24]. Before modeling, mice were trained for three consecutive days to find a hidden platform (120 s maximum trial time). Following 20 days of treatment, spatial probe tests measured swimming speed, platform crossings, and total distance swum within the target quadrant over 120 seconds.

TUNEL assay

Brain tissue damage was assessed via TUNEL staining using a commercial kit (40306ES50, YEASEN). Sections were dewaxed, incubated with Proteinase K and equilibration buffer, and then with TdT buffer for 60 minutes. After washing with PBS, sections were counterstained with DAPI and imaged under a fluorescence microscope [25, 26].

Hematoxylin-eosin (HE) staining

HE staining was performed to examine dopaminergic neuron morphology. Sections were baked at 60°C, dewaxed, rehydrated, stained with hematoxylin (5-10 min), rinsed, and counterstained with eosin (3-5 min). After dehydration and clearing in xylene, slides were sealed and examined microscopically [27].

Immunofluorescence

Immunofluorescence was used to detect NLRP3 expression. After antigen retrieval and blocking with 5% BSA, sections were incubated overnight at 4°C with a primary antibody against NLRP3 (30109-1-AP, Proteintech), followed by a fluorescent secondary antibody (90 min at

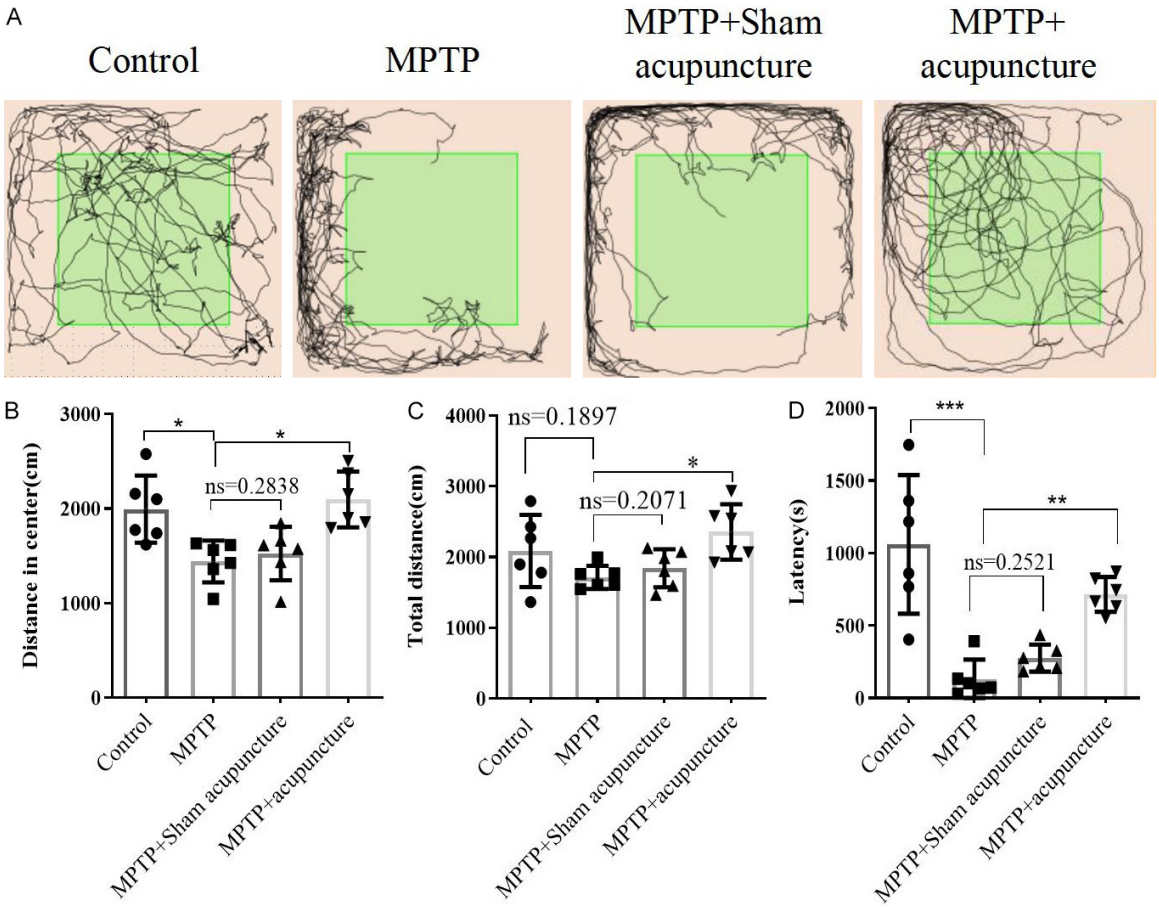

Figure 1. OFT and rotarod test. A. OFT tracking. B. Distance traveled in the center (cm) in OFT. C. Total distance (cm) in OFT. D. Latency time (s) in the rotarod test. *P < 0.05, **P < 0.01, ***P < 0.001. *Open field test (OFT),* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

37°C). DAPI was used to stain nuclei. Images were captured under a fluorescence microscope.

Western blot

Protein was extracted using RIPA buffer (P0-013B, Beyotime) and quantified by BCA assay (BL521A, Biosharp). Samples were separated by SDS-PAGE and transferred to PVDF membranes. Membranes were blocked with 5% skim milk and incubated overnight at 4°C with primary antibodies against tyrosine hydroxylase (TH, α-syn, NLRP3, IL-1β, IL-18, caspase-1, GSDMD, and GAPDH (all from Proteintech). Secondary HRP-conjugated antibodies (SA00-001-2/SA00001-1, Proteintech) were applied for 90 minutes. Signal detection was performed using ECL substrate (Advansta, K-12045-D50) and visualized using Chemiscope6100 (CLINX) [28].

Statistical analysis

Data were analyzed using GraphPad Prism 8.0 and expressed as mean ± standard deviation. One-way ANOVA was used for group comparisons. A P-value < 0.05 was considered statistically significant.

Results

EA alleviated motor dysfunction in PD mice

Behavioral tests were first conducted to assess motor function. As shown in **Figure 1A**, the MPTP group displayed a shorter distance in the center area in the OFT compared to the control group. Sham acupuncture did not significantly affect this parameter, whereas electroacupuncture markedly increased both the center distance and total distance traveled (**Figure 1B** and **1C**). In the rotarod test, the MPTP group

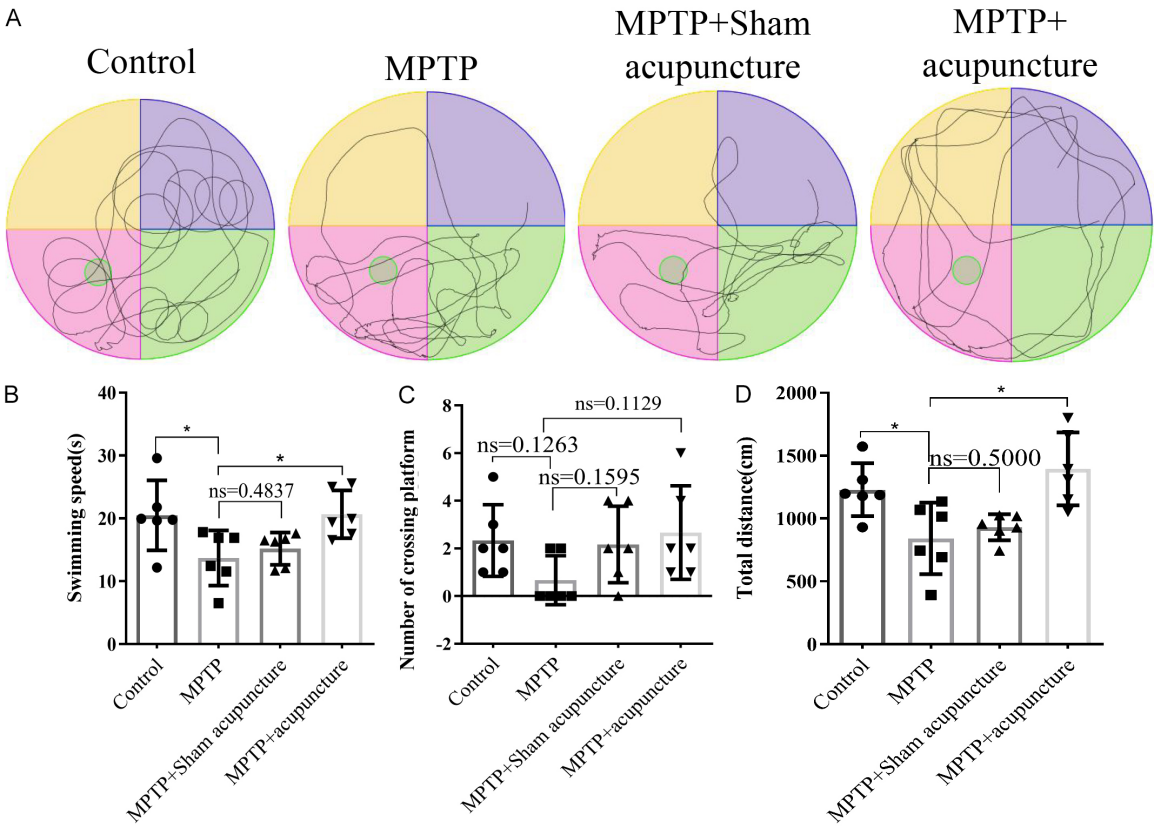

Figure 2. MWM test. A. MWM tracking. B. Swimming speed (s). C. Number of platform crossings. D. Total distance (cm). *$P < 0.05$. *Morris water maze (MWM),* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

exhibited reduced latency to fall, indicating impaired motor coordination. This impairment was not reversed by sham acupuncture but was significantly improved following electroacupuncture treatment, with prolonged latency times observed (**Figure 1D**).

Electroacupuncture enhances spatial learning and memory in PD mice

EA improved spatial learning memory in PD mice: The MWM test was conducted to evaluate spatial cognitive function. As illustrated in **Figure 2A**, the MPTP group exhibited reduced swimming speed and total distance compared to controls. Sham acupuncture had no effect, whereas electroacupuncture significantly increased both swimming speed and distance (**Figure 2B-D**).

EA decreased brain tissue damage in PD mice: Cell apoptosis Histopathological analysis revealed that staining for apoptosis was elevated in the brain in the MPTP group relative to the control group. No significant changes were observed after sham acupuncture; however, EA significantly reduced apoptosis levels (**Figure 3A**). HE staining showed increased neuronal damage in the MPTP group, which was not alleviated by sham acupuncture. In contrast, EA reduced histological signs of brain tissue damage (**Figure 3B**).

EA inhibited the NLRP3 inflammasome pathway: To investigate the molecular mechanism, we examined the expression of inflammasome-related proteins in the midbrain. The MPTP group showed decreased expression of TH and increased levels of α-synuclein (α-syn), NLRP3, IL-18, IL-1β, caspase-1, and GSDMD, indicating activation of the NLRP3 inflammasome pathway. These alterations were not significantly reversed by sham acupuncture. However, EA significantly increased TH expression and reduced the expression of α-syn, NLRP3, IL-18, IL-1β, and GSDMD (**Figure 4A** and **4B**).

Discussion

PD is the second most common neurodegenerative disorder and so far, it remains incur-

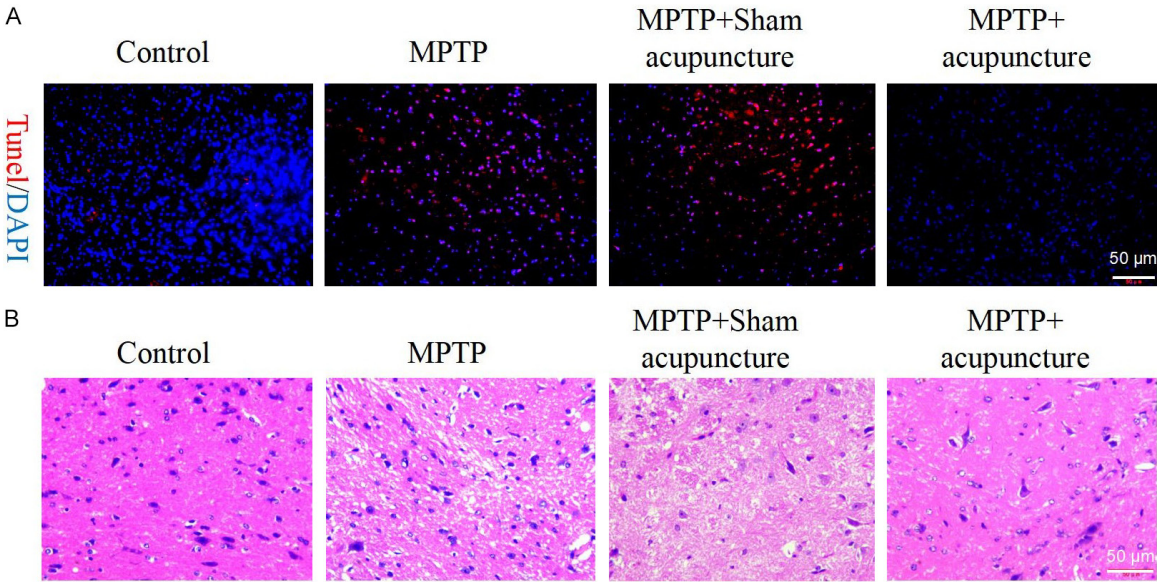

Figure 3. Evaluation of brain histopathology in PD mice. A. TUNEL detection of the apoptosis of brain tissue (n = 6). B. HE staining of the damage of brain tissue (n = 6). Parkinson's disease (PD), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

able. It is characterized by progressive neurological and motor impairments, accompanied by a range of non-motor symptoms that severely impact quality of life [29]. PD is marked by the gradual loss of dopaminergic neurons in the substantia nigra pars compacta [30]. Acupuncture has been shown to mitigate dopaminergic neuronal degeneration in PD models [31]. Compared to pharmacological treatments, acupuncture offers advantages such as high safety and minimal side effects, making it suitable for long-term use. However, the mechanisms underlying its effects remain poorly understood. In this study, a PD mouse model was established using MPTP, and EA treatment was applied. The results demonstrated that EA alleviated PD symptoms, in part by inhibiting the NLRP3 inflammasome pathway.

Neurotoxin-based PD models, especially those using MPTP, are widely used due to their close resemblance to the clinical features of PD [32]. MPTP induces neurotoxicity by impairing mitochondrial function, increasing oxidative stress, and promoting neuroinflammation and apoptosis-related protein expression [33]. It is metabolized by monoamine oxidase B into MPP+, which selectively damages nigrostriatal dopaminergic neurons [34]. Consequently, the progressive loss of dopamine in the striatum of the substantia nigra disrupts the extrapyramidal motor system, leading to motor dysfunction [35]. The MPTP model replicates key features of PD, including α-synuclein aggregation and reduced locomotion, as seen in the OFT [36]. Gao et al. demonstrated that echinacoside ameliorated MPTP-induced motor deficits, evidenced by increased OFT distance and improved performance in the rotarod test [37]. Based on these findings, the present study successfully established an MPTP-induced PD mouse model.

Traditional Chinese medicine considers PD a condition of "root deficiency and superficial excess" [38]. Internal deficiencies are primarily associated with the liver, spleen, and kidneys, while superficial symptoms involve wind, phlegm, fire, and blood stasis [39]. Acupuncture treatment for PD commonly target acupoints along the governor vessel, the hand Yangming large intestine meridian, and the foot Shaoyang gallbladder meridian [40], with Baihui (GV20), Hegu (LI4), and Taichong (LR3) being frequently used [41]. These points are believed to regulate qi and blood, restore internal organ harmony, and relieve PD symptoms. Baihui, located at the vertex of the head, is thought to gather Yang meridians and regulate Yin-Yang balance [42]. Hegu, the Yuan-source point of the large intestine meridian, is used to modulate qi and blood and calm the mind [43]. Taichong, the

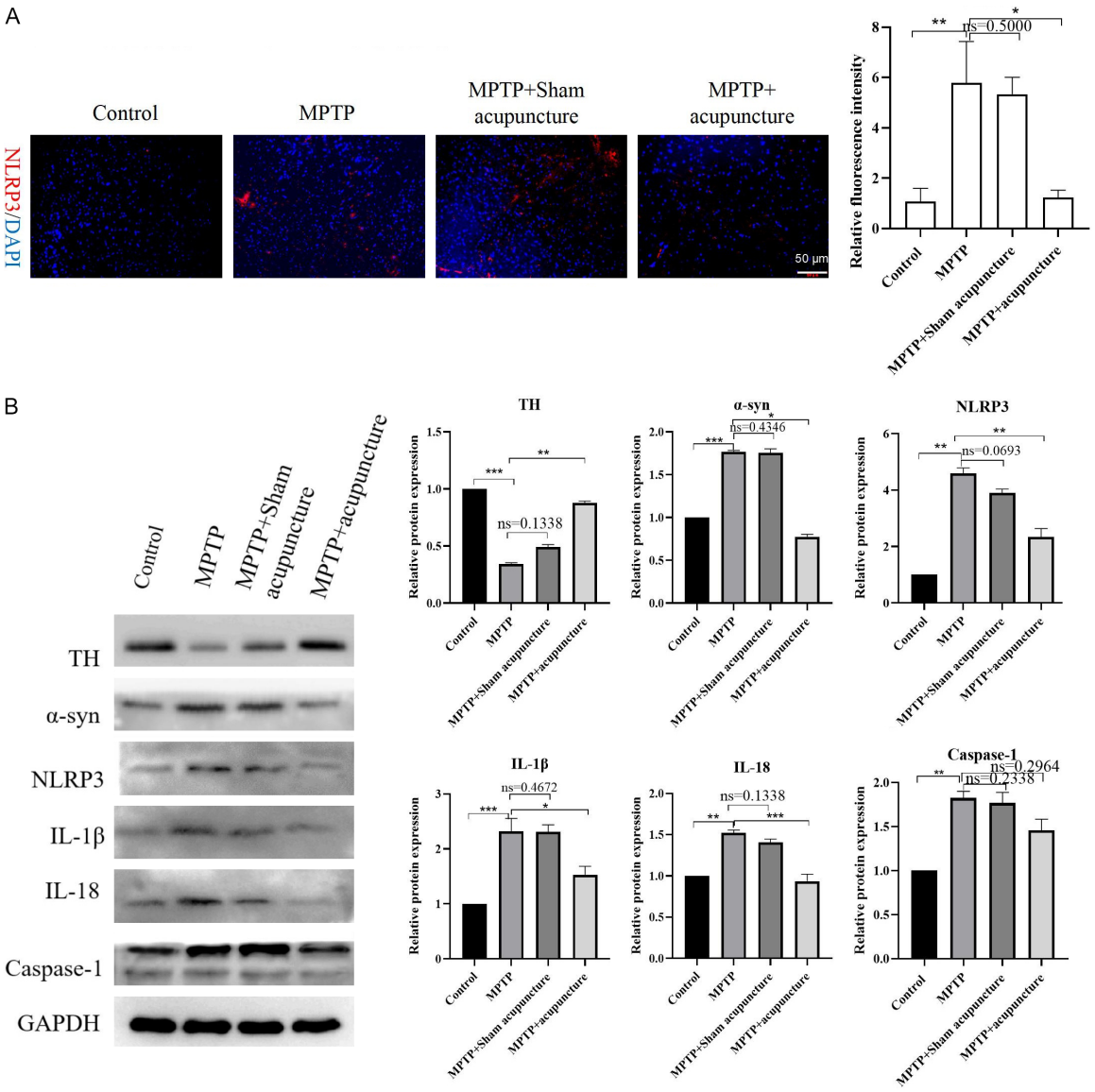

Figure 4. Electroacupuncture inhibited the NLRP3 inflammasome pathway. A. IF detection of NLRP3 expression in brain tissue (n = 6). B. Western blotting analysis of TH, α-syn, NLRP3, IL-18, IL-1β, Caspase-1, and GSDMD expressions (n = 6). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Yuan-source point of the liver meridian, is believed to soothe liver qi, extinguish internal wind, and eliminate phlegm and heat [44]. EA parameters-such as acupoint selection, stimulation frequency, current intensity, and duration-are critical for therapeutic efficacy [17]. This study employed Hegu, Baihui, and Taichong as acupoints for EA in MPTP-induced PD mice [19, 20].

Neuroinflammation, characterized by glial activation and the release of proinflammatory mediators, plays a key role in PD pathogenesis [45]. In particular, microglial activation is considered an early hallmark of PD [46, 47]. Activated microglia release cytokines that promote lymphocyte infiltration and exacerbate neuroinflammation, accelerating neuronal damage [48]. EA has been shown to inhibit microglial activation, suppress neuroinflammation, and attenuate dopaminergic neuronal loss during early PD [49]. Han et al. reported that EA improved MPTP-induced motor deficits in PD mice [17]. Consistent with their findings, the present study also demonstrated improved locomotor function and spatial learning memory

following EA. Previous research has similarly shown that EA enhances cognitive performance in mice [50].

The anti-apoptotic effects of acupuncture may be related to the upregulation of neurotrophic factors and downstream survival pathways [51]. Acupuncture exerts neuroprotective effects by increasing brain-derived neurotrophic factor, reducing oxidative stress, and inhibiting the degeneration of nigrostriatal neurons [52]. Neuroplasticity is also proposed as a mechanism linking acupuncture to functional recovery in neurological diseases [53]. Han et al. noted that EA preserved dopaminergic neurons in the substantia nigra in MPTP-treated mice [17], while Yeo et al. found that acupuncture enhanced dopaminergic neuron survival and reduced α-synuclein accumulation [54]. Furthermore, EA has been reported to alleviate neuronal injury and slow PD progression [55]. The present study confirmed these findings, showing that EA reduced MPTP-induced neuronal apoptosis and preserved dopaminergic neurons in PD mice. Collectively, these results highlight the therapeutic potential of EA at Hegu, Baihui, and Taichong acupoints for PD management.

Recent studies have shown that EA may modulate brain function via the gut-brain axis [56]. Alterations in gut microbiota can induce intestinal inflammation, contributing to PD progression [57]. One study demonstrated that EA at Hegu and Taichong promoted the restoration of microbial diversity in MPTP-induced PD mice and preserved enteric nervous system-associated bacterial species [17]. EA has also been shown to alleviate motor deficits in PD mice by regulating gut microbiota diversity [58]. Additionally, EA reversed the loss of intestinal microbial diversity, inhibited IL-6 and tumor necrosis factor-α (TNF-α)-mediated inflammation, and improved MPTP-induced behavioral impairments [17]. In a rotenone-induced PD rat model, EA suppressed Toll-like receptor 4 (TLR4) expression in the midbrain substantia nigra, reduced TNF-α and IL-6 levels, and mitigated neuroinflammatory responses, ultimately improving motor function [59].

Substantial evidence supports the involvement of α-synuclein (α-syn) overexpression and aggregation in PD pathogenesis [60]. α-Syn aggregation, the pathological hallmark of PD, is known to spread along the brain-gut axis [61]. Injection of preformed α-syn protofibrils into rodent brains has been shown to induce aggregation of endogenous α-syn, leading to neuronal dysfunction and cell death [62]. Thus, α-syn represents a critical biomarker and therapeutic target in PD. In the present study, EA at Hegu, Baihui, and Taichong acupoints significantly reduced α-syn expression in MPTP-induced PD mice.

PD is primarily characterized by the progressive loss of dopaminergic neurons in the substantia nigra [11]. Increasing attention has been paid to the role of neuroinflammation in PD, particularly the NLRP3 inflammasome, a multi-protein complex composed of NLRP3, ASC, and procaspase-1. Upon activation, NLRP3 mediates cleavage of pro-caspase-1 into active caspase-1, which in turn processes pro-IL-1β and pro-IL-18 into their mature forms [63, 64]. α-Syn aggregates can activate the NLRP3 inflammasome, triggering the release of IL-1β and IL-18 and promoting neuroinflammation [65]. NLRP3 activation has been implicated in motor impairment, dopaminergic neuronal degeneration, and α-syn accumulation in various PD animal models [66, 67]. Microglial NLRP3 activation may serve as a chronic driver of neuroinflammation and dopaminergic pathology [68], with α-syn acting both as a trigger and target in this pathway [69]. Conversely, inhibiting NLRP3 inflammasome assembly in familial and sporadic PD models protects dopaminergic neurons from degeneration [70]. Thus, the NLRP3 inflammasome represents a promising therapeutic target in PD.

Our study demonstrated that EA at Hegu, Baihui, and Taichong acupoints inhibited the NLRP1/NLRP3 inflammasome pathway in MPTP-induced PD in mice. These findings suggest that EA may confer neuroprotection via suppression of inflammasome-mediated neuroinflammation. However, this study did not directly confirm whether EA alleviates PD progression through NLRP3 inhibition, highlighting a limitation. Further validation using rescue experiments is warranted. Moreover, given the absence of animal models that fully recapitulate the pathological features, clinical symptoms, and disease course of human PD, our findings serve as a preliminary reference for future translational research.

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Disclosure of conflict of interest

None.

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