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Preoperative inflammatory pain exacerbates postoperative pain and neurocognitive impairment

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ABSTRACT

Aims: Many studies have shown that postoperative pain aggravates perioperative neurocognitive disorder (PND). In this study we aimed to clarify the effect of preoperative inflammatory pain on postoperative pain and cognitive function.

Methods: We established the inflammatory pain model by injected complete freund adjuvant (CFA) and the PND model by tibial fracture surgery in 14- month-old C57BL/6 mice. The paw withdrawal threshold and body weight of the mice were measured 7 days before surgery and 3 days after surgery. On the third postoperative day, mice were subjected to behavioral testing or sacrificed to collect brain tissue.

Results: The result shows that CFA exacerbated postoperative pain and cognitive dysfunction in mice, enhanced surgery-induced activation of microglia and astrocytes in the hippocampus, and increased surgery-induced the overexpression of IL-1β, IL-6, and TNF-α, as well as aggravated the decreased expression of α7nAChR and the overexpression of HMGB1 in the hippocampus induced by surgery.

Conclusion: Our study shows that preoperative inflammatory pain further aggravates postoperative pain and neurocognitive dysfunction in aged rats, and the mechanism may be related to neuroinflammation caused by α7nAChR-mediated CAP dysfunction and high release of HMGB1.

1. Introduction

Perioperative neurocognitive disorders (PNDs), such as acute delirium and long-term cognitive decline, are common postoperative complications among the elderly (Evered et al., 2018). These complications can occur hours to days after surgery and result in permanent deficits in executive function, memory, and other cognitive areas (Kong et al., 2022). PNDs increase mortality, medical expenses, and pose a significant burden on patients' families and society (Evered et al., 2022).

Although the cause of PND has not been fully understood, previous studies have shown that postoperative pain exacerbates postoperative cognitive dysfunction (Koyama et al., 2019; Zhao et al., 2021; Zywiel et al., 2014). However, these studies have mainly focused on postoperative pain and disregarded preoperative pain. Preoperative pain affects 30 % of people worldwide, and persistent pain is associated with poor cognitive performance (Cohen et al., 2021; Bell et al., 2022). Some studies have linked preoperative pain to postoperative cognitive function (Huai et al., 2021; Ding et al., 2021; Gu et al., 2019), but further research is necessary to support these conclusions. A clinical study has also shown that preoperative pain affects postoperative pain processes (Ozgür et al., 2011). Thus, the present study aims to investigate the effects of preoperative pain on postoperative pain and cognitive function to clarify PND risk factors.

PNDs' mechanisms are complex, with neuroinflammation being the main mechanism underlying their occurrence and development (Li et al., 2022). α7nicotinic acetylcholine receptor (α7nAChR) is a principal subtype of the nicotinic acetylcholine receptor superfamily and a crucial regulator of the cholinergic anti-inflammatory pathway (CAP) in the brain (Wu et al., 2021). Its expression in astrocytes and microglia and its ability to modulate anti-inflammatory cytokines make this receptor a novel therapeutic target for neuroinflammatory regulation (Piovesana et al., 2021a). α7nAChR dysfunction in the hippocampus

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after surgery is a key event in PND's neuroinflammation development (Liu et al., 2017). It also mediates the pain transmission process (Bagdas et al., 2018). High mobility group box 1 (HMGB1) is a critical marker of neuroinflammation and a common biological marker of neurodegenerative diseases associated with neuroinflammation (Paudel et al., 2018), regulated by α7nAChR (Li et al., 2016). Therefore, the study hypothesizes that preoperative pain's effects on postoperative pain and cognitive function may be related to α7nAChR dysregulation and HMGB1 activation.

To investigate this hypothesis, we used an inflammatory pain model to induce preoperative pain and performed tibial surgery to establish the PND model. And we observed the neuroinflammatory response and measured the expression of α7nAChR and HMGB1 in the hippocampus to explore the underlying mechanisms.

2. Materials and methods

2.1. Animals

Male C57BL/6 mice aged 12–14 months and weighing 30–35 g were obtained from the Experimental Animal Center of Zhejiang Province, China. The experimental protocol was approved by the Animal Care and Use Committee of Ningbo University, and all procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health. The mice were housed in a controlled environment maintained at 22–24 °C with a 12-hour light/dark cycle

2.2. Modeling

2.2.1. Inflammatory pain model

As previously outlined, we instigated the inflammatory pain model by injecting 20 μL of complete Freund's adjuvant (CFA) (F5881, Sigma-Aldrich) into the left hind paw of the mice (Hua et al., 2022). For the control group, an equivalent volume of saline was injected into the same paw.

2.2.2. PND model

The anesthesia and surgical procedures were conducted in line with our prior methodology (Yuan et al., 2022). To briefly summarize, anesthesia was induced using 3 % sevoflurane, and then maintained at 2 % sevoflurane using a R500SE device from RWD Life Science, Shenzhen, China. Subsequent to shaving and disinfecting the left lower limb of the mice, an open tibial fracture operation was performed. This involved making a median incision on the left hind paw, drilling a hole in the tibia, and inserting a 0.38-mm needle into the intramedullary canal. The muscle was separated, an osteotomy was conducted at the lower third of the tibia, and the skin was sutured with 4/0 Prolene. Local injection of ropivacaine provided pain relief, while topical application of erythromycin ointment prevented infection. After recovering from anesthesia, the mice were returned to their cages.

2.3. Experimental groups

All animals were randomly assigned to one of four groups: (1) control (CON), (2) surgery (SUR), (3) CFA (CFA), and (4) CFA+surgery (CFA+SUR). To eliminate any confounding effects of paw withdrawal threshold (PWT) on subsequent behaviors, some animals in each group were sacrificed after completing the PWT test for brain tissue biochemical evaluation, while others skipped the PWT and proceeded directly to later behavioral testing. The experimental workflow is depicted in Fig. 1.

2.4. Behavioral tests

The behavioral tests took place in a room with subdued lighting.

2.4.1. Nociceptive behavior test: PWT

The mechanical pain threshold was evaluated using von Frey filaments, following the "up-down" method outlined by Bonin et al. (2014). Mice were acclimated in plastic boxes (7 ×9 ×7 cm^3) with metal mesh bottoms for 30 minutes before the experiment. Von Frey filaments ranging from 0.02 to 2.0 were then applied vertically to the plantar surface of the left hind paw. A positive response was recorded if the mouse exhibited brisk withdrawal or paw flinching. Each mouse underwent stimulation at 10-minute intervals.

2.4.2. Open field (OF) test

The OF test was employed to assess motor ability and anxiety levels in mice, as detailed previously (Meng et al., 2019). On the third day post-surgery, mice were placed in a 40 × 40 × 40 cm^3 open-field box. The floor of the box was divided into 16 squares, with the central area (20 ×20 cm^2) comprising four squares and the remaining forming the edge area. Mice were consistently positioned in the box for each trial, allowing them to freely explore for 5 minutes. Their behavior was recorded and analyzed using VisuTrack software (Xinruan Information, Shanghai, China). The total distance traveled by the mice was used as a measure of motor ability, while the time spent in the central area indicated their level of anxiety.

2.4.3. Fear conditioning (FC) test

As mentioned earlier, the Fear Conditioning (FC) test was utilized to evaluate learning and memory (Meng et al., 2019). On the 6th day post-surgery, the mice were introduced into a conditioning chamber (30 ×30 ×45 cm^3, SuperFcs, Xinruan Information) for a 180-second exploration period. Subsequently, the mice were exposed to a conditioned stimulus in the form of an auditory cue (70 dB, 3 kHz). Following the termination of the tone, a 2-second foot shock (0.75 mA) was administered as an unconditioned stimulus, with the process being repeated after 60 seconds. After a 24-hour interval, the mice were placed back in the same environment for a 3-minute period, without the auditory cue or foot shocks, and their freezing behavior was recorded using SuperFcs to evaluate contextual fear memory. Two hours later, changed environment of the chamber , and mice were placed with the same auditory stimulation for another 3 minutes, their freezing behavior

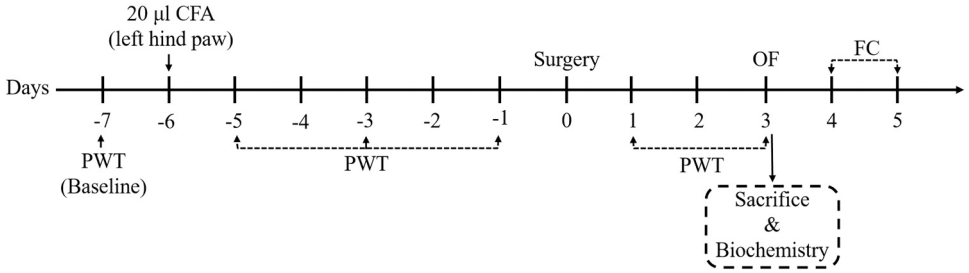

Fig. 1. Schematic of the experimental process.

was recorded to assess cued fear memory.

2.5. Body weight (BW) measurement

Prior research has indicated a correlation between variations in mice BW and alterations in pain perception (Wheat and Cooper, 2009; Roughan et al., 2016). Consequently, in the present study, BW measurements were taken following each PWT test to serve as an indicator of pain intensity levels experienced by the mice.

2.6. Biochemical analysis

Given that the hippocampus plays a key role in both pain processing and cognitive functions such as learning and memory (Cohen et al., 2021; Ding et al., 2021; Yuan et al., 2022; Meng et al., 2019). It is also a key region involved in neuroinflammation following surgery or pain (Koyama et al., 2019; Zhao et al., 2021; Li et al., 2022; Yuan et al., 2022). Therefore, the hippocampus was chosen as a target for our investigation of the molecular mechanisms underlying the exacerbation of postoperative pain and cognitive dysfunction in our model.

2.6.1. Western blot (WB)

The established protocol (Yuan et al., 2022) was meticulously executed. Hippocampal tissue was homogenized, and the resulting lysate was allowed to cool on ice for 30 minutes. The supernatant was carefully extracted through centrifugation at 12000 rpm, 4 °C for 10 minutes. Subsequently, proteins were meticulously separated using 8–12 % sodium dodecyl sulfate-polyacrylamide gel electrophoresis, followed by their transfer onto polyvinylidene fluoride membranes. These membranes were then blocked at room temperature for 30 minutes. Next, the membrane underwent primary antibody probing with rabbit anti-α7nAChR (1:1000, 21379–1-AP, Proteintech), rabbit anti-HMGB1 (1:1000, GB11103, Servicebio), and rabbit anti-β-actin (1:1000, GB15003, Servicebio). Subsequent incubation with the secondary antibody, goat anti-rabbit IgG (1:5000, GB23303, Servicebio), was carried out. An enhanced chemiluminescence detection kit was employed for visualizing and quantifying the intensity of the immunoreactive bands using optical density analysis. The relative protein levels were then normalized to those of β-actin.

2.6.2. Immunohistochemistry

The immunohistochemistry method was performed in accordance with previously established procedures (Yuan et al., 2022). Following anesthesia, the mice underwent perfusion with normal saline and 4 % paraformaldehyde (PFA) via cardiac perfusion. The brain tissue was then removed and fixed in 4 % PFA for 24 hours. Subsequently, the brain tissue was immersed in 15 % and 30 % sucrose solution for 24 hours and sliced into 25-μm-thick sections. These sections were then incubated at 4 °C overnight in 0.1 M phosphate-buffered saline (PBS) buffer containing 0.5 % Triton X-100 and primary antibodies, rabbit Anti-Iba1 (1:100, ab178846, Abcam) and mouse anti-GFAP (1:500, GB12096, Servicebio). This was followed by incubation with the corresponding secondary antibodies, 488-conjugated goat anti-rabbit (1:400, GB25303, Servicebio) and 488-conjugated goat anti-mouse (1:400, GB25301, Servicebio).The quantification of Iba-1- and GFAP-positive cells was carried out using ImageJ software (NIH, USA). Images of the slices were captured using a confocal laser scanning microscope (SP8, Leica, Frankfurt, Germany), and the positive area in the field was analyzed using ImageJ software. Both image acquisition and quantification were performed in a blinded manner.

2.6.3. Enzyme-linked immunosorbent assay (ELISA)

In line with our prior research (Yuan et al., 2022), the levels of hippocampal interleukin-1 beta (IL-1β; EK201B/3–01, Multi Sciences), IL-6 (EK206/3–01, Multi Sciences), and tumor necrosis factor-alpha (TNF-α; EK282/4–01, Multi Sciences) were determined using the prescribed protocols provided with the respective ELISA kits. The concentrations were quantified and reported in pg/mg.

2.7. Statistical analysis

The statistical analysis was conducted using SPSS 22.0 software (Chicago, IL, USA). The data were presented as the mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was used, followed by the application of Bonferroni's post-hoc test. A significance level of $P < 0.05$ was considered as indicating a statistically significant difference.

3. Results

3.1. Preoperative inflammatory pain exacerbated lower mechanical pain threshold and weight loss in postoperative mice

Compared to the CON and SUR groups, the PWT of mice in the CFA and CFA+SUR groups was significantly decreased on the 5th, 3rd, and 1st day before surgery (Fig. 2A), indicating a successful establishment of the inflammatory pain model. Compared to the CON group, the PWT of the mice in the SUR group decreased significantly on the 1st postoperative day but returned to normal levels on the 3rd postoperative day. These results suggested that surgery-induced pain is most severe on the 1st postoperative day and resolves on the 3rd postoperative day (Fig. 2A). Compared to the SUR and CFA groups, the PWT in the CFA+SUR group mice was significantly lower after surgery (Fig. 2A), indicating that preoperative inflammatory pain further aggravates the postoperative pain.

Compared to the CON groups, mice in the SUR group showed BW loss on the 1st postoperative day and returned to baseline on the 3rd postoperative day (Fig. 2B), consistent with the pain threshold trend (Fig. 2A). The BW of mice in the CFA and CFA+SUR groups decreased significantly from the 3rd day before surgery, and the BW in the CFA+SUR group continued to decrease on the 3rd day after surgery, while the CFA group recovered and differed significantly from the CFA+SUR group (Fig. 2B).

3.2. Preoperative inflammatory pain enhanced cognitive deficits in postoperative mice

In the OF test, no difference was observed in the average speed of the four groups of mice, indicating that the exercise ability of the mice had recovered on the 3rd postoperative day (Fig. 3A). Compared to the CON groups, mice in the CFA group spent significantly less time in the central area but not in the SUR group (Fig. 3B, C), indicating that the inflammatory pain, but not surgery, caused depression in the mice. Mice in the CFA+SUR group showed lower central area time than those in the CFA and SUR groups (Fig. 3B, C), indicating that the preoperative inflammatory pain and surgery together aggravated depression in mice.

In the FC test of contextual and cued fear memory, the freezing time of the SUR group was significantly lower than that of the CON group, while the freezing time of the CFA+SUR group was significantly lower than the SUR and CFA groups (Fig. 3D, E). This finding indicated that neurocognitive impairment occurred in mice after surgery, and preoperative inflammatory pain could aggravate this postoperative neurological injury.

3.3. Preoperative inflammatory pain promoted surgery-induced activation of microglia and astrocytes in the hippocampus

Enhanced activation of glial cells in the brain is a major step in neuroinflammatory response; therefore, the activation of microglia and astrocytes in the CA3 regions of the hippocampus was observed on the 3rd day after surgery (Fig. 4A, B). Compared to the CON group, the percentage of Iba-1-positive and GFAP-positive cells was significantly

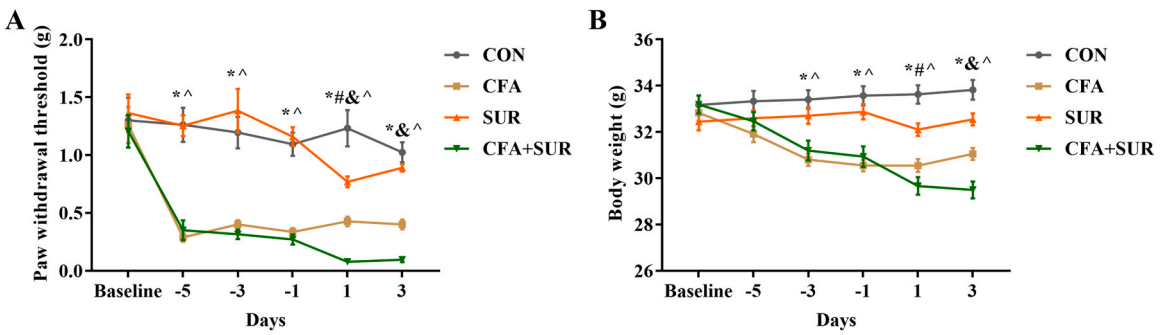

Fig. 2. Effects of CFA and surgery on mechanical pain threshold and BW in mice. (A) The changing trend of PWT of mice in each group. (B) The changing trend of BW of mice in each group. Data are depicted as the mean ± standard error (n = 10). $^{*}P<0.05$ CFA group versus CON group; $^{\#}P<0.05$ SUR group versus CON group; $^{\&}P<0.05$ CFA+SUR group versus CFA group; $^{\wedge}P<0.05$ CFA+SUR group versus SUR group.

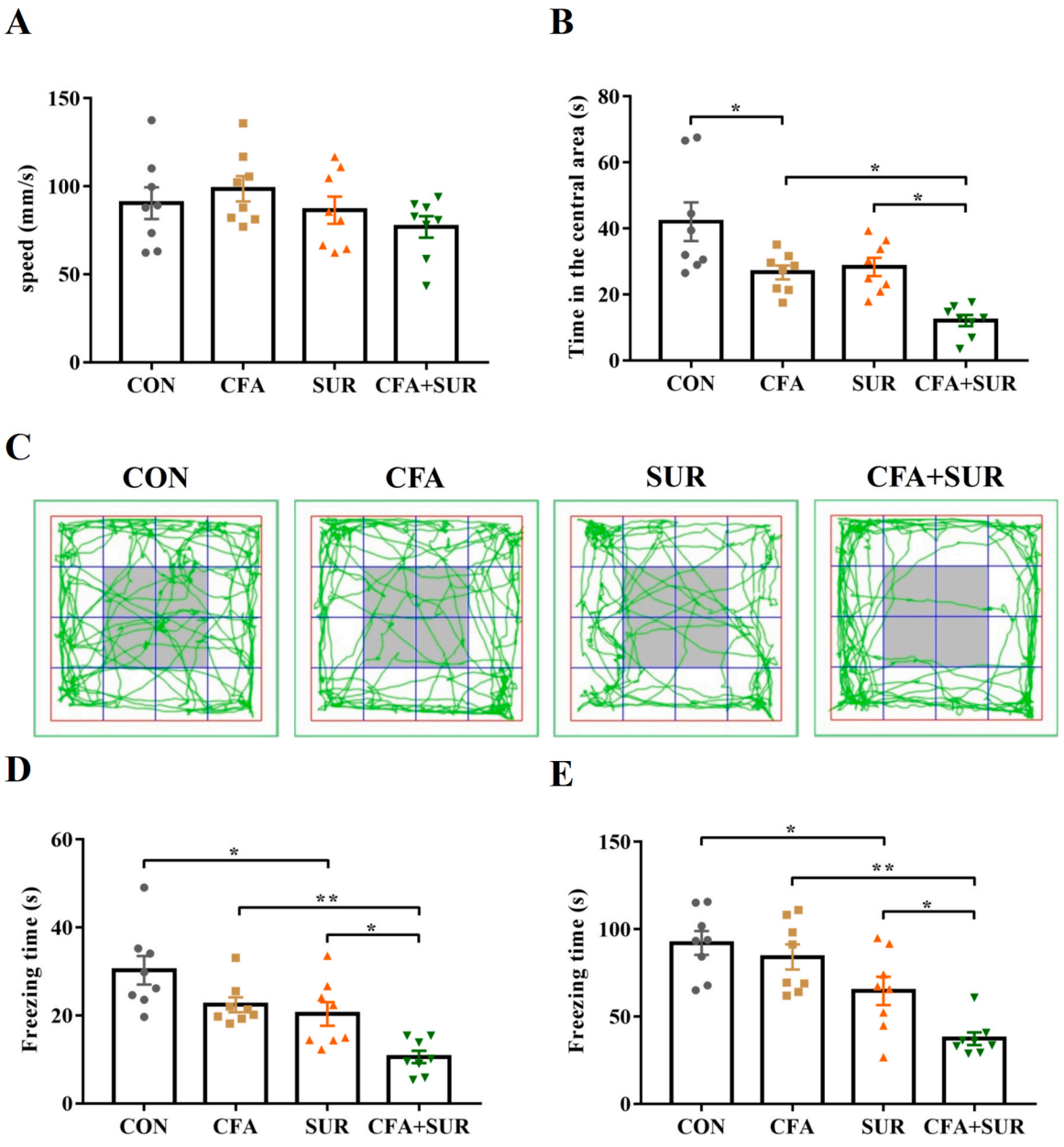

Fig. 3. Effects of CFA and surgery on neurocognitive function in mice. (A) The average speed in OF test. (B) The time in the central area in OF test. (C) Representative images of movement track in OF test. (D) The freezing time of the contextual fear memory in FC test. (E) The freezing time of the cued fear memory in FC test. Data are depicted as the mean ± standard error (n = 8). $^{*}P<0.05$; $^{**}P<0.01$

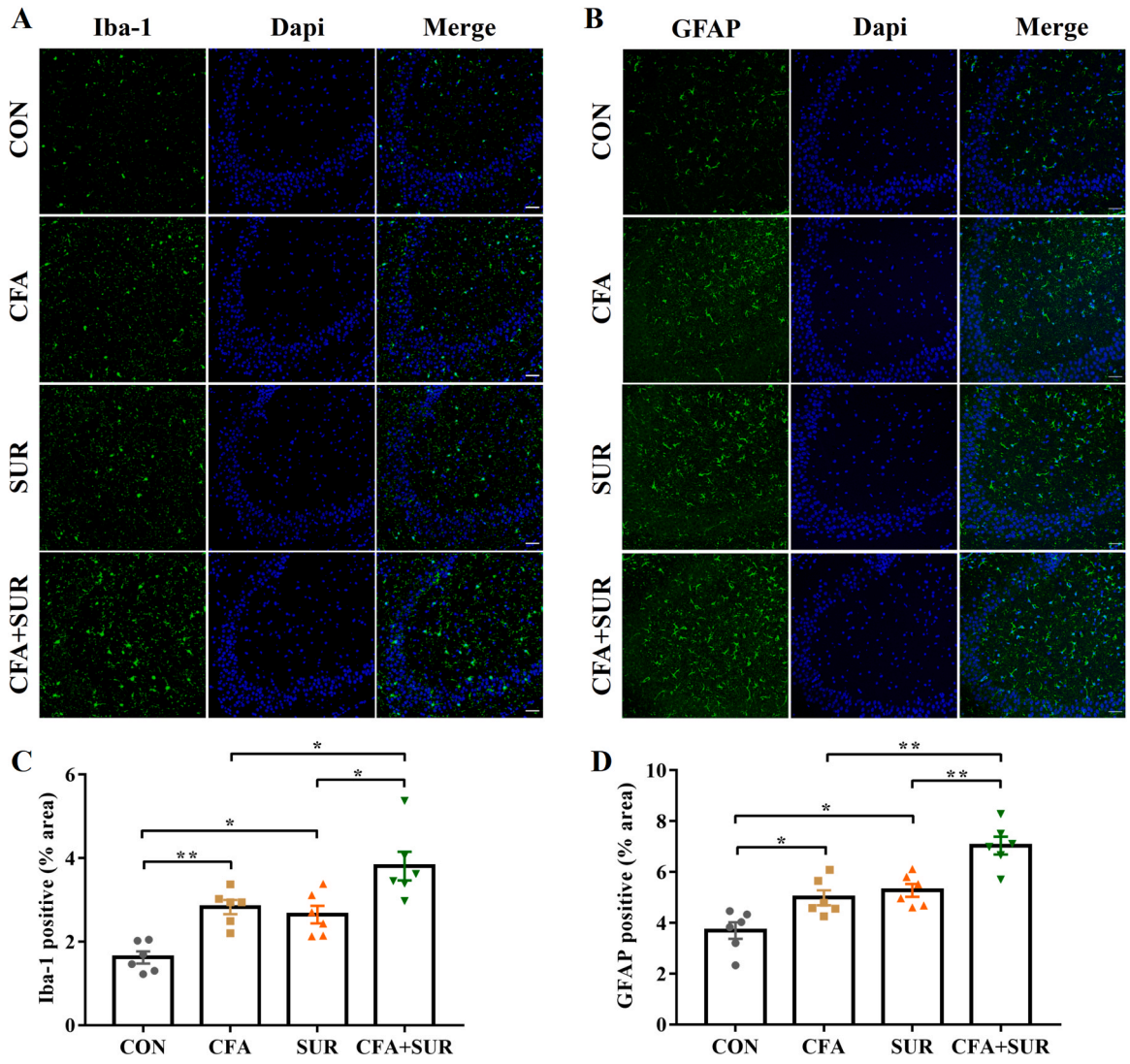

Fig. 4. Effects of CFA and surgery on the activation of microglia and astrocytes in the CA3 regions of the hippocampus. (A) Representative confocal microscopy analysis of Iba-1-positive microglia in the hippocampus. Scale bar 50μm. (B) Representative confocal microscopy analysis of GFAP-positive astrocytes in the hippocampus. Scale bar 50μm. (C) Quantitative of the percentage of Iba1-positive microglia area. (D) Quantitative of the percentage of GFAP-positive astrocytes area. Data are depicted as the mean ± standard error (n = 6). *$P < 0.05$; **$P < 0.01$.

increased in the CFA and SUR groups (Fig. 4C, D). Compared to the SUR group, a higher percentage of Iba-1- and GFAP-positive cells was observed in the CFA+SUR group (Fig. 4C, D).

3.4. *Preoperative inflammatory pain exacerbated surgery-induced neuroinflammation in the hippocampus*

Neuroinflammation is closely related to both PND and pain. Therefore, the expression of IL-1β, IL-6, and TNF-α after surgery was observed

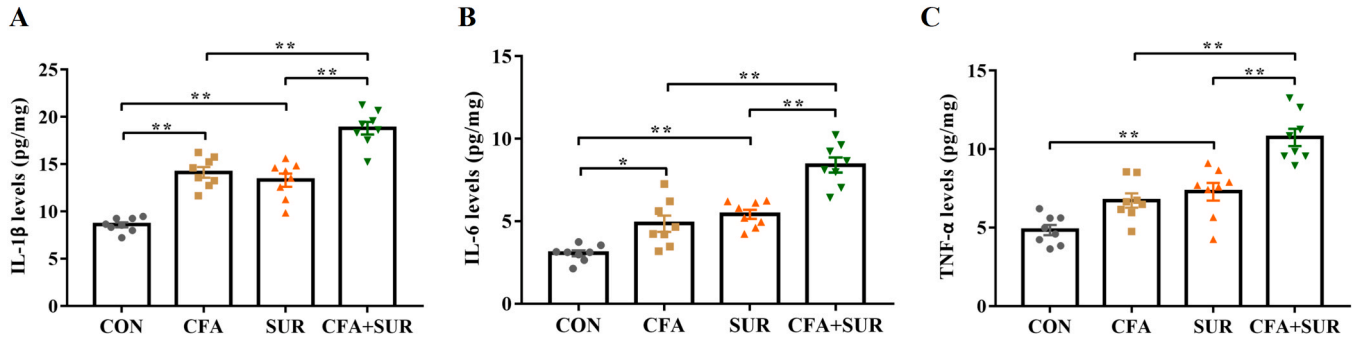

Fig. 5. Effects of CFA and surgery on the neuroinflammation in the hippocampus. (A) Expression of IL-1β in the hippocampus. (B) Expression of IL-6 in the hippocampus. (C) Expression of TNF-α in the hippocampus. Data are depicted as the mean ± standard error (n = 8). *$P < 0.05$; **$P < 0.01$.

by ELISA to evaluate the neuroinflammation after surgery. The results showed that CFA significantly increased the expression of IL-1β and IL-6, and surgery significantly increased the expression of IL-1β, IL-6, and TNF-α in the hippocampus (Fig. 5A, B, and C). In addition, CFA significantly increased the release of surgery-induced IL-1β, IL-6, and TNF-α (Fig. 5A, B, and C).

3.5. *Preoperative inflammatory pain aggravated the decreased expression of α7nAChR and the overexpression of HMGB1 in the hippocampus induced by surgery*

Brain α7nAChR and HMGB1 are the key mediators of the occurrence and development of neuroinflammation. Therefore, WB was used to detect the expression of α7NachR and HMGB1 in the hippocampus (Fig. 6A). We observed that both CFA and surgery significantly decreased α7nAChR expression and increased HMGB1 expression (Fig. 6B, C). Also, α7nAChR was significantly lower in the CFA+SUR group than in the SUR group, while HMGB1 expression was significantly higher than in the SUR group (Fig. 6B, C).

4. Discussion

Pain and cognition have been the focus of research regarding their correlation. A study using functional magnetic resonance imaging found that painful stimuli reduce activity in the right anterior hippocampus and functional connectivity between associated task areas, leading to slower response times and hindering early memory formation (Forkmann et al., 2013). Studies on older adults have shown that persistent pain is linked to poor cognitive performance, highlighting the importance of pain management in maintaining cognition and reducing dementia risk (Bell et al., 2022). A longitudinal cohort study found a 7.7 % increased risk of dementia in older adults with persistent pain (Whitlock et al., 2017). Preclinical studies have demonstrated that CFA-induced inflammatory pain impairs spatial learning and memory functions (Mohammadi et al., 2020). In line with these findings, our study showed that CFA induced depression behavior and decreased fear memory in mice. Importantly, we found that preoperative inflammatory pain worsens surgically-induced neurocognitive decline. Given the higher prevalence of preoperative pain in older adults who are less likely to recover from chronic pain (Cohen et al., 2021; Whitlock et al., 2017), it may be a key factor contributing to the high incidence of perioperative neurocognitive disorders in elderly patients.

Previous studies have explored the impact of preoperative pain on perioperative neurocognitive disorders (PND) (Huai et al., 2021; Ding et al., 2021; Gu et al., 2019), but they often overlooked the evaluation of postoperative pain. However, evidence suggests that the pathophysiology of PND may be linked to postoperative pain, and adequate postoperative analgesia has been shown to reduce the incidence of PND (Kristek et al., 2019; Gan et al., 2020). Preclinical studies have also demonstrated that acute postoperative pain can worsen neurocognitive impairment in elderly rats (Koyama et al., 2019; Zhao et al., 2021). Considering these findings, it is important to understand the relationship between preoperative pain and PND by examining the influence of preoperative pain on postoperative pain (Wheat and Cooper, 2009; Roughan et al., 2016). In our study, we assessed pain using both a pain threshold test and body weight changes, as they are correlated with pain. We found that preoperative inflammatory pain aggravated postoperative pain and body weight loss in mice, consistent with clinical research findings (Ozgür et al., 2011). Therefore, we suggested that the perioperative pain management for the prevention of PND should start from preoperative and not just postoperative.

The pathogenesis of perioperative neurocognitive disorders (PND) involves peripheral inflammatory factors triggered by surgery that communicate with the brain, leading to neuroinflammation characterized by an abundance of proinflammatory cytokines and overactivation of glial cells, this process is considered a key mechanism in PND development (Li et al., 2022; Yang et al., 2020). Studies have linked high levels of IL-1β, IL-6, TNF-α, and other inflammatory factors to PND (Meng et al., 2019; Hu et al., 2018; Sun et al., 2014; Lu et al., 2022), with inhibiting these factors showing potential to reverse PND-related behavioral changes (Yuan et al., 2022; Liu et al., 2021). Pain plays a role in the perioperative inflammatory response (Franchi et al., 2017; Vergne-Salle and Bertin, 2021; Sommer et al., 2018), impacting pain regulation and cognitive function post-surgery. Recent research emphasizes the significance of pain-related glial cells, such as astrocytes and microglia (Wang and Xu, 2022; Finnerup et al., 2021), in mediating pain sensations (Miyamoto et al., 2017). In this study, preoperative inflammatory pain increased inflammatory cytokine levels and activated microglia and astrocytes in the hippocampus, while surgical stimulation further intensified neuroinflammation, contributing to worsened cognitive deficits post-surgery.

Numerous studies have established a link between pain and cognition, with overlapping neuroanatomy and neurochemical matrix between the two systems (Bushnell et al., 2013) , which is a major reason why pain affects patients' cognitive function. The α7nAChR-based cholinergic anti-inflammatory pathway (CAP) has been identified as crucial in pain and cognition (Bagdas et al., 2018; Gamage et al., 2020), with studies indicating that selective α7nAChR agonists can alleviate abnormal pain and reverse neuroinflammation and neurodegeneration in chronic neuropathic pain models (Pacini et al., 2010). Meanwhile, decreased α7nAChR expression in the hippocampus is linked to neuroinflammation in PND (Wei et al., 2022). Our findings showed that CFA and surgery decreased α7nAChR expression in the hippocampus, which may contribute to the pain-PND interaction. α7nAChR mediates anti-inflammatory responses via two intracellular signaling pathways: Jak2/STAT3 and PI3K/Akt, which negatively regulate the nuclear factor NF-kB responsible for proinflammatory cytokine expression and glial activation (Wu et al., 2021; Piovesana et al., 2021a). This effect is likely

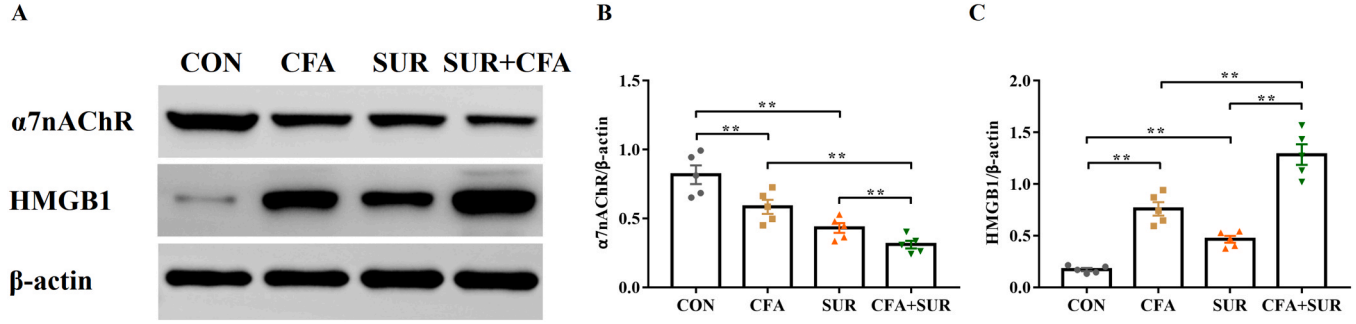

Fig. 6. Effects of CFA and surgery on hippocampal α7nAChR and HMGB1 expression. (A) Immunoblot bands of α7nAChR and HMGB1 in the hippocampus of mice. (B) Quantitative analysis of gray value of α7nAChR immunoblotting. (C) Quantitative analysis of gray value of HMGB1 immunoblotting. Data are depicted as the mean ± standard error (n = 5). *$P < 0.05$; **$P < 0.01$.

mediated through vagal nerve reflex connections. The vagus nerve is involved in a peripheral neuroimmune response, evidence suggests that such neuroimmune signals may be transmitted to higher centers, including the hippocampus, to regulate the central CAP (Suarez et al., 2018; Onimus et al., 2024). This hypothalamic cholinergic signaling reduces pro-inflammatory cytokines both centrally and peripherally, and it requires an intact vagus nerve (Zhai et al., 2017). Higher vagal nerve activity is associated with an increased number of α7nACh receptors in neural tissue, indicating a relationship between vagal innervation and α7nACh receptor expression (Ma et al., 2025). The positive regulatory mechanisms of the vagus nerve can alleviate neuroinflammation, and several studies have shown that vagus nerve stimulation can improve PND by inhibiting neuroinflammation (Xie et al., 2025). Research suggests that the gut-brain axis via the vagus nerve plays a role in impairments of planning and spatial working memory in CFA mice (Yue et al., 2023), and α7nAChR KO mice exhibit depression-like behaviors in a vagus nerve-dependent manner (Zhang et al., 2016; Pu et al., 2021). These studies indicate that there are also negative regulatory mechanisms associated with the vagus nerve by gut-brain axis. In this study, CFA-induced pain may have reduced α7nAChR expression in the brain through the negative feedback regulation of the vagus nerve.

HMGB1, a cytokine mediator implicated in neuroinflammation and PND (Saxena et al., 2021). Studies have shown that inhibiting HMGB1 secretion by activating α7nAChR-related CAP, improving survival rates in sepsis models (Wang et al., 2004) and attenuating hyperoxia-induced acute inflammatory lung injury (Sitapara et al., 2020). Our results indicate that α7nAChR regulates HMGB1 in the inflammatory pain and PND model and that their expression trend in the hippocampus is opposite. A7nAChR agonists have been shown to exert anti-inflammatory effects and modulate neuroinflammation (Piovesana et al., 2021b), which could potentially counteract the neuroinflammatory processes observed in our study. A7nAChR agonists have been shown to be beneficial in central nervous system disorders characterized by cognitive deficits, such as Alzheimer's disease and schizophrenia (Vallés and Barrantes, 2023). In addition, there is growing evidence that α7nACh receptor agonists and modulators hold promise for the treatment of chronic inflammatory pain (Luo and Huang, 2024). In light of the above studies, we plan to further investigate the role of α7 nAChR agonists in reducing postoperative pain and cognitive dysfunction in future studies, especially in the context of preoperative inflammatory pain. This will be an important next step in expanding our understanding of the underlying mechanisms and potential treatments for postoperative neuroinflammation and cognitive impairment.

5. Conclusions

In conclusion, our results indicate that preoperative inflammatory pain can exacerbate postoperative pain and neurocognitive dysfunction in aged mice undergoing surgery. The neuroinflammation triggered by α7nAChR-mediated CAP dysfunction and HMGB1 release in the hippocampus appears to play a crucial role in this process. These findings highlight the importance of addressing preoperative pain in elderly patients, not just postoperative pain, as it is essential for reducing the incidence of perioperative neurocognitive disorders (PND) and improving the overall quality of life in this population.

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CRediT authorship contribution statement

Ming Qianyu: Validation, Data curation. **Ji Yiqin:** Supervision, Methodology. **chen junping:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Formal analysis, Data curation. **Wang Qiusheng:** Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Xing Xiuzhong:** Data curation, Conceptualization. **Wang Ruichun:** Data curation, Conceptualization. **Liu Rongjun:** Data curation, Conceptualization. **Sun Daofan:** Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Yuan Hui:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Meng Bo:** Visualization, Validation, Data curation, Conceptualization. **Lu Bo:** Writing – original draft, Visualization, Validation, Data curation, Conceptualization.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None.

Author contributions

HY, DS, QW and JC participated in the design of the experiment, HY, DS, BM, BL, RL, XX and RW participated in the experimental operation, HY, DS and YJ conducted a statistical analysis of the experimental data, HY, DS, QW and JC were responsible for writing the manuscript. HY and DS contributed equally to this work.

Data availability statement

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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