Pioglitazone prevents sevoflurane-induced neuroinflammation and cognitive decline in a rat model of chronic intermittent hypoxia by upregulating hippocampal PPAR-γ

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Abstract. Post-operative cognitive dysfunction is a common complication after anesthesia and surgery. Sevoflurane (SEV), a widely used inhalational anesthetic, can exaggerate neuroinflammation and cause cognitive dysfunction under chronic intermittent hypoxia (CIH) conditions by down-regulating hippocampal peroxisome proliferator-activated receptor-γ (PPAR-γ). In the present study, it was examined whether treatment with PPAR-γ agonist pioglitazone (PIO) is beneficial in counteracting SEV-induced neuroinflammation and cognitive decline in a rat model of CIH. Rats were exposed to CIH for 4 weeks. After 2 weeks of CIH, these animals underwent either 2.6% SEV or control (CON) exposure for 4 h. PIO (60 mg/kg) or vehicle (VEH) was administered orally twice daily for 2 weeks, starting one day prior to SEV or CON exposure. Compared with CIH-CON+VEH rats, CIH-SEV+VEH rats exhibited significant cognitive decline as indicated by increased latency to locate the hidden platform and shorter dwell-time in the goal quadrant in the Morris Water Maze task. Molecular studies revealed that CIH-SEV+VEH rats had increased proinflammatory cytokine expression and microglial activation in the hippocampus, which were associated with decreased PPAR-γ activity. Notably, SEV-induced cognitive decline and increases in proinflammatory cytokine expression and microglial activation were prevented by PIO, which increased hippocampal PPAR-γ activity. PIO also increased hippocampal PPAR-γ activity in CIH-CON rats but did not alter proinflammatory cytokine expression and microglial activation as well as cognitive function. Additionally, expression of hippocampal PPAR-α and PPAR-β, two other PPAR isotypes, were comparable among the groups. These data suggest that PIO prevents SEV-induced exaggeration of neuroinflammation and cognitive decline under CIH conditions by upregulating hippocampal PPAR-γ. PIO may have the potential to prevent anesthetic SEV-induced cognitive decline in surgical patients with obstructive sleep apnea.

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Introduction

Post-operative cognitive dysfunction (POCD) generally refers to the decline in cognitive ability after anesthesia and surgery when compared to preoperative cognitive status (1). POCD can occur in nearly 10% of all surgical patients and 40% of elderly patients at the point of discharge, and the long-term impact of this is marked by a significantly higher mortality rate than age and sex-matched controls without POCD (1). Although the causes of POCD are not fully understood, accumulating evidence from experimental and clinical studies has shown that general anesthesia alone is capable of causing cognitive dysfunction (2). It is worth noting that anesthesia-induced cognitive dysfunction may depend on the types of anesthetic agents, drug doses, exposure duration and patient age (3,4). In addition, the presence of a pathological condition may increase the susceptibility to developing POCD or exacerbate the pre-existing cognitive impairment after anesthesia (5-7). Neuroinflammation in the brain, particularly in the hippocampus, has been shown to play a contributory role in the pathogenesis of cognitive dysfunction, including POCD (8-10). Microglia, the resident innate immune cells in the brain, are major sources of pro-inflammatory cytokines (11). Activation of microglia in the brain results in the release of pro-inflammatory cytokines, which triggers the neuroinflammatory response and subsequently leads to neuronal damage and losses (11-13). Interventions that inhibit microglia activity and neuroinflammation in the brain can significantly ameliorate cognitive dysfunction in multiple neurodegenerative diseases (8,14).

Obstructive sleep apnea, characterized by repeated occlusions of the pharyngeal airway during sleep, is a devastating

respiratory control disorder and is associated with serious and adverse consequences including cognitive dysfunction and dementia (15,16). It is widely accepted that chronic intermittent hypoxia (CIH), a cardinal feature of obstructive sleep apnea, plays an important role in cognitive dysfunction in obstructive sleep apnea (17). CIH can induce activation of microglia and subsequent neuroinflammation in the hippocampus, a key region of the brain associated with spatial learning and memory acquisition, contributing to cognitive dysfunction (15,18).

Peroxisome proliferator-activated receptor-γ (PPAR-γ) belongs to the PPAR family of ligand-activated transcription factors that is well-known to regulate adipocyte differentiation, fatty acid storage and glucose metabolism (19). In addition, PPAR-γ plays an important role in the immune response through its ability to inhibit the expression of inflammatory cytokines and to direct the differentiation of immune cells towards anti-inflammatory phenotypes (20-22). In the brain, activation or upregulation of PPAR-γ has been demonstrated to inhibit the synthesis and release of pro-inflammatory cytokines in many central nervous system diseases in which massive inflammation plays a detrimental role (23-25). Notably, PPAR-γ is expressed in multiple cell types in the brain including microglia, astrocytes and neurons (26,27), and relatively high PPAR-γ expression levels have been found in the brain areas associated with learning and memory including the hippocampus (26,27). Sevoflurane (SEV) is one of the most widely used anesthetic agents for induction and maintenance of general anesthesia in surgical patients, including patients with obstructive sleep apnea. Studies from our laboratory and others have recently demonstrated that a moderate duration of SEV (2-3% for 2 or 4 h) does not cause neuroinflammation in the hippocampus and cognitive impairment in either adult or aged animals (4,28-30). However, SEV downregulates PPAR-γ expression and activity in the hippocampus, which increase the sensitivity and susceptibility to CIH insult, leading to aggravated microglia activation and neuroinflammation as well as exaggeration of cognitive decline under CIH conditions (28). Pioglitazone (PIO) is a thiazolidinedione (TZD) class synthetic PPAR-γ agonist and has been used for the treatment of patients with type II diabetes mellitus. In addition, PIO exhibits anti-inflammatory and neuroprotective effects in multiple inflammatory central nervous system disorders (31,32). PIO can cross the blood-brain barrier (33). The present study was designed to examine whether treatment with PPAR-γ agonist PIO would upregulate PPAR-γ expression and activity in the hippocampus, preventing SEV-induced cognitive decline in a rat model of CIH.

Materials and methods

Animals. A total of 60 male Sprague-Dawley rats weighing 200-250 g (8-9 weeks of age) were purchased from Beijing Laboratory Animal Research Center (Beijing, China) and maintained on a 12:12 h light/dark cycle at room temperature (23±2˚C) in 50-60% relative humidity with *ad libitum* access to food and water. All experimental protocols were approved by the Animal Care and Use Committees of Shandong University and conducted in accordance with the guidelines of the Animal Care and Use Committee at Shandong University (Jinan, Shandong, China).

Protocol. Rats were placed into a plastic cage equipped with the intermittent hypoxia apparatus and exposed to intermittent hypoxia for 4 weeks, as previously described (28). The hypoxia/re-oxygenation profile was run for eight consecutive hours during the 12 h of light cycle each day to coincide with the animal sleep cycle. During each cycle of intermittent hypoxia, the oxygen concentration in the cage dropped from 21 to 5% over a 50-sec period and was then quickly returned to 21% during the following 40 sec. Constant room air was given to the cages during the 12 h of the dark cycle each day. After 2 weeks of intermittent hypoxia, CIH rats underwent either control (CON, room air) or a moderate duration of SEV (2.6%) exposure for 4 h, and were treated with vehicle (VEH, distilled water) or PPAR-γ agonist PIO for 2 weeks, starting one day prior to CON or SEV exposure. The experimental groups were as follows (n=15 for each group): i) CIH-CON+VEH, ii) CIH-CON+PIO, iii) CIH-SEV+VEH, and iv) CIH-SEV+PIO. SEV exposure was conducted as previously described (28). Briefly, animals assigned to SEV exposure were placed in a temperature-controlled chamber that was equipped with an anesthesia device and a multi-gas monitor. SEV (2.6%) was provided by a humidified 30% O_2 carrier gas from a calibrated vaporizer for 4 h. Animals assigned to CON exposure were also placed in the same chamber for 4 h but no SEV was provided. After CON or SEV exposure, all animals were returned to their original cages and underwent CIH for another 2 weeks. PIO (60 mg/kg) or VEH was administered twice daily by oral gavage, as described previously (31). At the end of the study protocol, spatial learning and memory in some animals (n=9 for each group) were examined using the Morris Water Maze test. Immediately after Morris Water Maze examination, some of the animals were sacrificed by decapitation under deep pentobarbital anesthesia and brains were quickly collected for molecular analyses. The rest of the animals (n=6 for each group) were transcardially perfused with saline containing heparin (1 U/ml) and then with 4% paraformaldehyde in 0.1 M phosphate buffer (PB) for immunofluorescent study. The experimental procedures and the timeline are shown in Fig. 1A.

Morris water maze task. Spatial learning and memory were examined using the Morris Water Maze after 4 weeks of intermittent hypoxia, as previously described (28). The spatial acquisition trial was performed over four consecutive days and each acquisition trial section consisted of four trials with an interval of 15 min. A rat was placed gently into the water facing the wall of the pool and allowed 120 sec to find a hidden escape platform submerged approximately 1 cm below the water surface. The time for each rat spent to locate the submerged platform was recorded as the escape latency. A probe trial was conducted 24 h after completion of the spatial acquisition trial to assess the spatial reference memory. During the probe test, the platform was removed from the pool and rats were allowed to swim freely for 120 sec in any of the four quadrants of the swimming pool. The percentage of time spent in the target quadrant where the platform had been placed was calculated as a measure of memory for platform position.

Western blot analysis. The rat brains were dissected and bilateral hippocampal tissues were quickly removed. Hippocampal

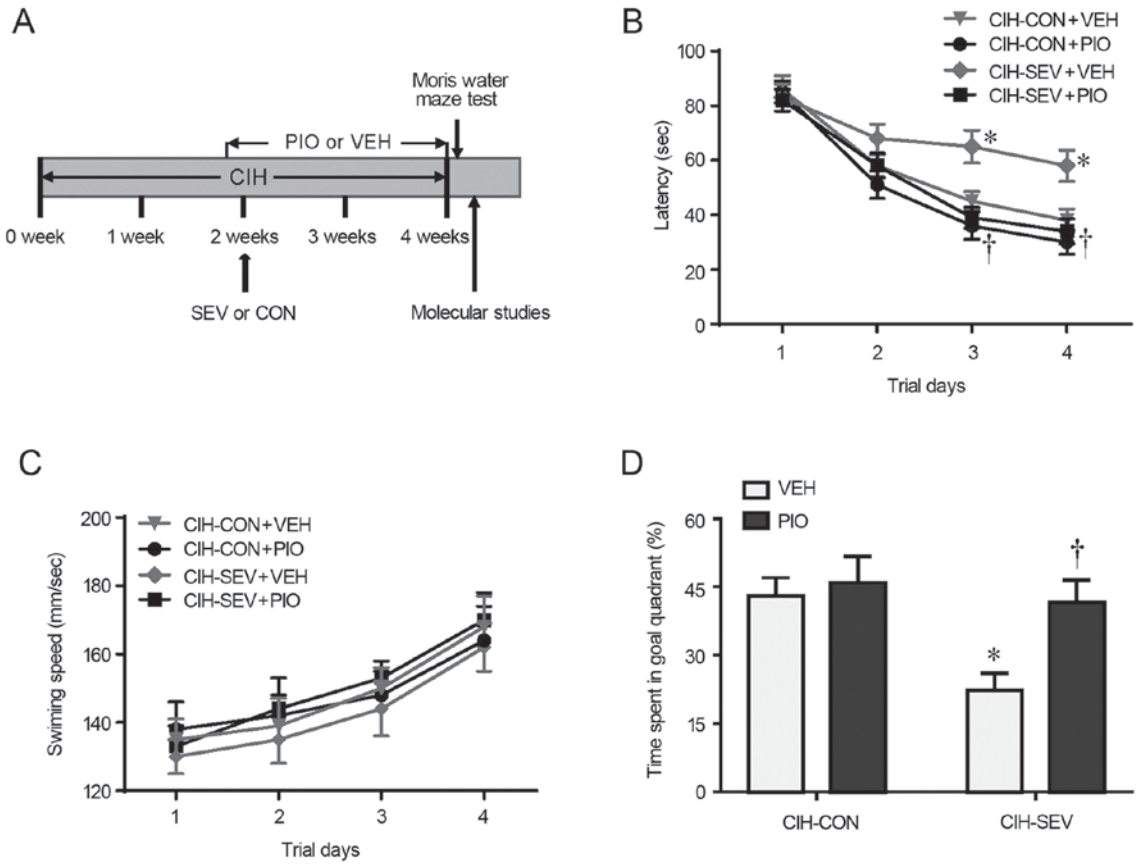

Figure 1. (A) Summary of the experimental procedures and timeline. (B-D) Effects of pioglitazone (PIO) treatment on sevoflurane (SEV)-induced cognitive decline in the CIH rats. Compared with the CIH-CON rats treated with VEH (CIH-CON+VEH), CIH-SEV rats treated with VEH (CIH-SEV+VEH) exhibited increased latency to locate the hidden platform (B) and shorter dwell-time in the goal quadrant (D) in Morris Water Maze task. PIO treatment reduced the escape latency and increased dwell-time in the goal quadrant in the CIH-SEV rats. Notably, the swimming speed was similar across the four experimental groups (C). Data are expressed as the mean ± SEM (n=9 per group). *P<0.05 vs. CIH-CON+VEH; †P<0.05, CIH-SEV+PIO vs. CIH-SEV+VEH. CIH, chronic intermittent hypoxia; CON, control; VEH, vehicle.

tissues were homogenized in cold lysis buffer (Beyotime Institute of Biotechnology, Shanghai, China) containing protease inhibitors. The proteins extracted from the hippocampal tissues were loaded onto 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and then transferred to polyvinylidene fluoride membranes. The membranes were immunoblotted with primary antibodies to tumor necrosis factor (TNF)-α (1:200; sc-52746), interleukin (IL)-1β (1:200; sc-52012), PPAR-γ (1:100; sc-7273), PPAR-α (1:100; sc-398394), PPAR-β (1:200; sc-74517) and β-actin (1:1,000; sc-47778) (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) at 4˚C overnight and then incubated with HRP-conjugated secondary antibodies (1:5,000; sc-2031) (Santa Cruz Biotechnology, Inc.) for 1 h at room temperature. The immunoreactive bands were visualized using enhanced chemiluminescence detection system (GE Healthcare, Chicago, IL, USA) and analyzed with ImageJ software version 1.49v (NIH; National Institutes of Health, Bethesda, MD, USA). All data were normalized to β-actin.

Determination of PPAR-γ activity. Nuclear extracts were prepared from the hippocampal tissues with a Nuclear Extract Kit (Active Motif, Carlsbad, CA, USA). PPAR-γ DNA binding activity was measured using Transcription Factor Assay Kit (Active Motif) following the manufacturer's instructions.

Immunofluorescence study. Immunofluorescence staining for microglia was performed as previously described (28). Briefly, perfused brains were removed and post-fixed in 4% paraformaldehyde at 4˚C overnight followed by incubation in 30% sucrose for 48 h at 4˚C. After being embedded in optimal cutting temperature (OCT), the brains were serially sectioned at 20-μm intervals using a cryostat microtome. The sections were immunostained at 4˚C overnight with anti-CD11b primary antibody (MCA275R; Chemicon, Temecula, CA, USA) that recognizes both non-activated and activated microglia, and were then incubated with a secondary antibody (Alex Fluor 488; A-11001, Invitrogen Thermo Fisher Scientific, Inc., Waltham, MA, USA) for 2 h at room temperature. Fluorescence images were acquired using a Zeiss LSM 510 confocal microscope at 40x magnification and the number of total and activated microglia were counted in several 0.2x0.2 mm squares. Activated microglia were presented as a percentage of the total number of microglia.

Statistical analysis. All data are presented as the mean ± standard error of the mean. A two-way analysis of variance followed by Bonferroni's post hoc test was performed for statistical analysis using GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA). Statistical significance was accepted at P<0.05.

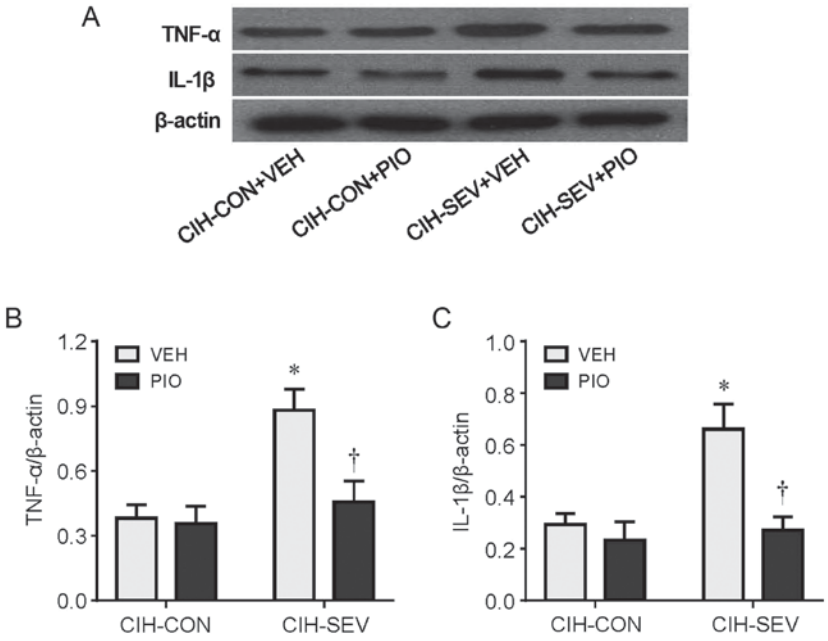

Figure 2. Effects of pioglitazone (PIO) treatment on sevoflurane (SEV)-induced neuroinflammation in the hippocampus in the CIH rats. Compared with the CIH-CON rats treated with VEH (CIH-CON+VEH), CIH-SEV rats treated with VEH (CIH-SEV+VEH) had increased expression of TNF-α (A and B) and IL-1β (A and C), which was inhibited by PIO treatment. Data are expressed as the mean ± SEM (n=9 per group). *P<0.05 vs. CIH-CON+VEH; †P<0.05, CIH-SEV+PIO vs. CIH-SEV+VEH. CIH, chronic intermittent hypoxia; CON, control; VEH, vehicle.

Results

Effects of PIO treatment on SEV-induced cognitive decline. Four weeks after intermittent hypoxia and 2 weeks after CON or SEV exposure, the Morris Water Maze task was performed to assess spatial learning and reference memory in each mouse group. As shown in Fig. 1B, CIH-SEV rats treated with VEH (CIH-SEV+VEH) exhibited significantly longer latency to find the hidden platform on the last two trials when compared with the CIH-CON rats treated with VEH (CIH-CON+VEH). A 2-week PIO treatment, starting one day prior to CON or SEV exposure, did not alter the escape latency in the CIH-CON rats, but it significantly reduced the escape latency in the CIH-SEV rats to an extent similar to that observed in the CIH-CON rats. Notably, the swimming speed across four experimental groups was comparable throughout 4 consecutive days (Fig. 1C). Probe trial showed that the percent time spent in the target quadrant was markedly reduced in the CIH-SEV rats treated with VEH (CIH-SEV+VEH) as compared to the CIH-CON rats treated with VEH (CIH-CON+VEH) (Fig. 1D). Compared with the respective VEH groups, PIO treatment significantly increased the percent time spent in the target quadrant in the CIH-SEV rats but not in the CIH-CON rats.

Effects of PIO treatment on SEV-induced neuroinflammation in the hippocampus. To examine the effect of PIO treatment on neuroinflammation, the protein levels of TNF-α and IL-1β, two key proinflammatory cytokines in the hippocampus, were assessed. Compared with the CIH-CON rats treated with VEH, CIH-SEV rats treated with VEH had significantly increased protein levels of both TNF-α (Fig. 2A and B) and IL-1β (Fig. 2A and C) in the hippocampus. Importantly, the increases in protein levels of TNF-α and IL-1β observed in the CIH-SEV rats were inhibited by PIO treatment, which did not alter these proinflammatory cytokines in the CIH-CON rats.

Effects of PIO treatment on SEV-induced microglial activity in the hippocampus. Immunofluorescence study revealed that the number of total microglia in the hippocampus was comparable among the four experimental groups (Fig. 3A and B). However, the number of activated microglia that were distinguished by strong CD11b immunoreactivity, an enlarged cell body, and fewer and shorter hypertrophic processes extending from the soma, was markedly higher in the hippocampus in the CIH-SEV rats treated with VEH compared with CIH-CON rats treated with VEH (Fig. 3A and C). Compared with the respective VEH groups, PIO treatment did not change the number of activated microglia in the CIH-CON rats, but it significantly reduced the number of activated microglia in the CIH-SEV rats.

Effects of PIO treatment on PPAR isoform expression and activity in the hippocampus. To determine whether PIO treatment prevented exaggerated microglia activation and neuroinflammation by upregulating hippocampal PPAR-γ, hippocampal PPAR-γ expression and activity were further evaluated. PPAR-γ protein levels (Fig. 4A) and its DNA binding activity (Fig. 4B) in the hippocampus were significantly decreased in the CIH-SEV rats treated with VEH compared with the CIH-CON rats treated with VEH. Interestingly, PIO treatment markedly increased PPAR-γ expression and its DNA binding activity in both the CIH-CON and CIH-SEV rats when compared with their respective VEH groups. Of note, there were no significant differences in expression of PPAR isoforms PPAR-α (Fig. 5A and B) or PPAR-β (Fig. 5A and C) among the four experimental groups.

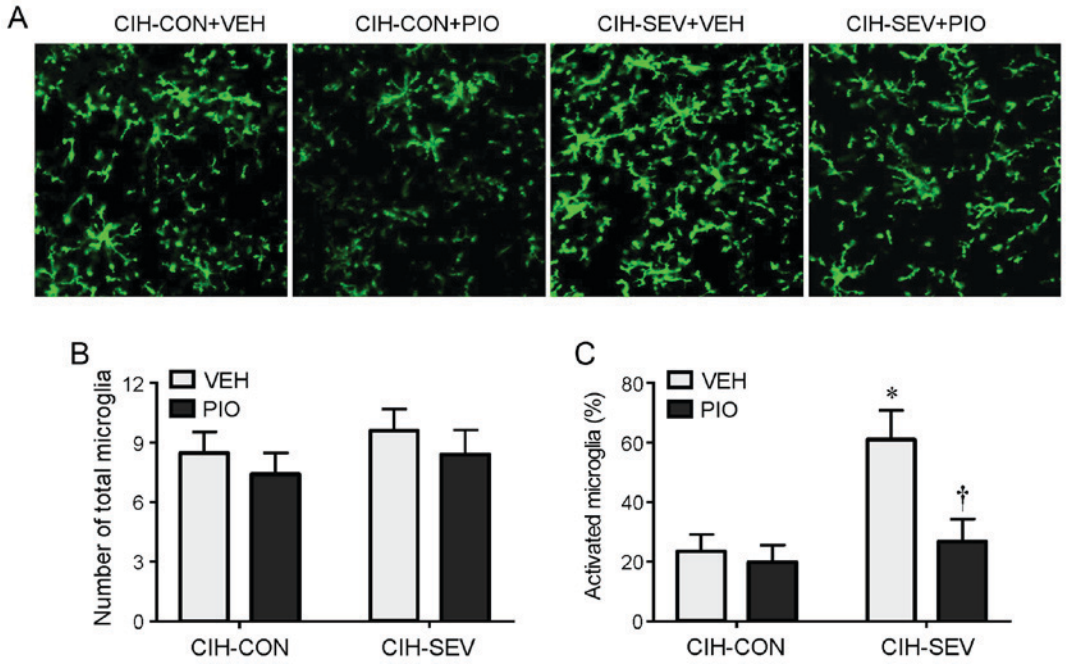

Figure 3. Effects of pioglitazone (PIO) treatment on sevoflurane (SEV)-induced microglial activity in the hippocampus in CIH rats. (A) Representative photomicrographs showing CD11b-immunoreactive microglia in the hippocampus in each group. Images were acquired at x40 magnification. (B) There was no difference in the total number of microglia across groups. (C) The number of activated microglia was higher in the CIH-SEV rats treated with VEH but was reduced in the CIH-SEV rats treated with PIO. Data are expressed as the mean ± SEM (n=6 per group). *P<0.05 vs. CIH-CON+VEH; †P<0.05, CIH-SEV+PIO vs. CIH-SEV+VEH. CIH, chronic intermittent hypoxia; CON, control; VEH, vehicle.

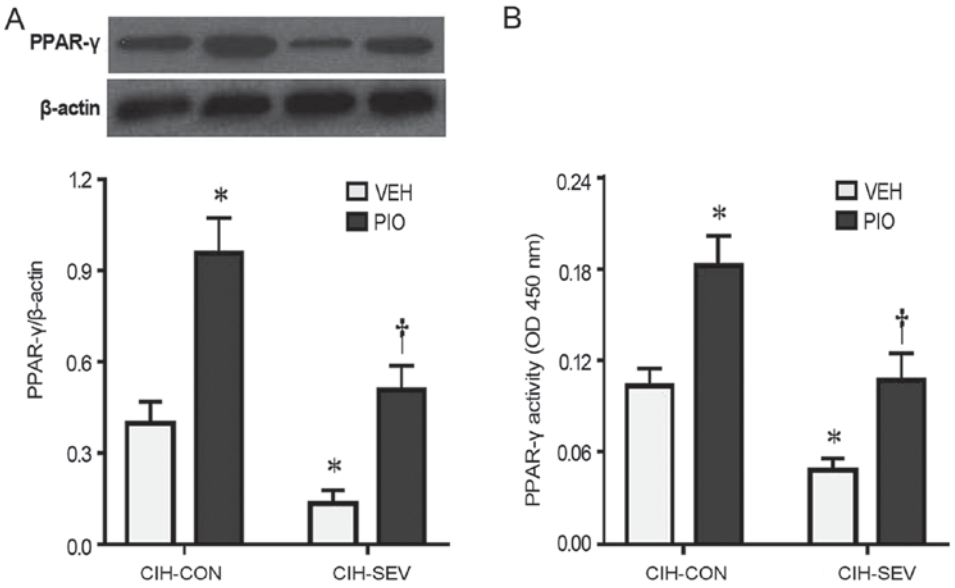

Figure 4. Effects of pioglitazone (PIO) treatment on expression (A) and activity (B) of PPAR-γ in the hippocampus in the CIH rats. Compared with the CIH-CON rats treated with VEH, CIH-SEV rats treated with VEH had decreased expression and activity of PPAR-γ. PIO treatment increased expression and activity of PPAR-γ in both the CIH-CON and CIH-SEV rats. Data are expressed as the mean ± SEM (n=9 per group). *P<0.05 vs. CIH-CON+VEH; †P<0.05, CIH-SEV+PIO vs. CIH-SEV+VEH. PPAR, peroxisome proliferator-activated receptor; CIH, chronic intermittent hypoxia; CON, control; VEH, vehicle.

Discussion

The major finding of the present study is that systemic administration of PPAR-γ agonist PIO upregulated hippocampal PPAR-γ expression and activity, inhibited anesthetic SEV-induced hippocampal microglia activation and neuroinflammation, and prevented SEV-induced cognitive decline in a rat model of CIH.

Obstructive sleep apnea is increasing in prevalence although it still remains significantly underdiagnosed (34). Patients with obstructive sleep apnea subjected to surgery are at increased risk for a wide variety of postoperative complications including cognitive decline, which should be recognized and managed in the perioperative period to minimize postoperative complications. We and others have previously reported that exposure to a moderate duration of SEV in animals did not

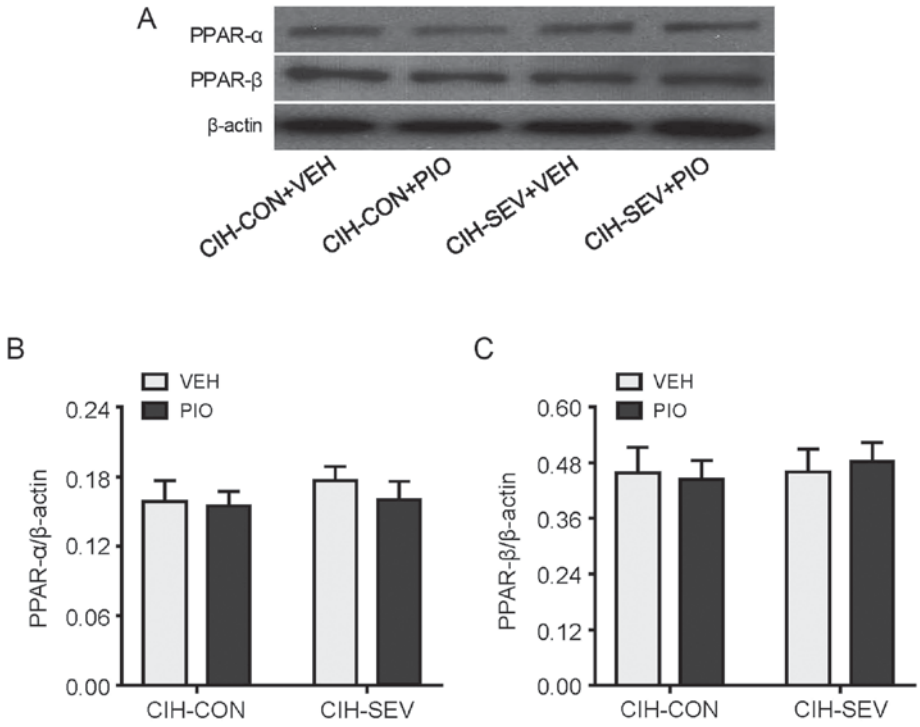

Figure 5. Effects of pioglitazone (PIO) treatment on expression of PPAR isoforms PPAR-α (A and B) and PPAR-β (A and C) in the hippocampus in the CIH rats. There were no differences in expression of PPAR-α or PPAR-β among the four groups. Data are expressed as the mean ± SEM (n=9 per group). PPAR, peroxisome proliferator-activated receptor; CIH, chronic intermittent hypoxia; CON, control; VEH, vehicle.

impair cognitive function under physiological conditions, but it induced cognitive decline under CIH conditions (28-30). In the present study, it was found that CIH-SEV rats treated with VEH exhibited decline in both spatial learning and memory in the Morris Water Maze task when compared with CIH-CON rats treated with VEH. These observations are consistent with previous reports (28), suggesting that a moderate duration of SEV causes cognitive decline in animals under CIH conditions.

Our previous study (28) demonstrated that SEV exaggerated microglia activity and neuroinflammation in the hippocampus, which were associated with reductions in hippocampal PPAR-γ expression and activity. In the present study, the number of activated microglia and proinflammatory cytokine expression were increased but PPAR-γ expression and activity were decreased in the hippocampus in CIH-SEV rats treated with VEH, compared with CIH-CON rats treated with VEH. These results confirm previous findings, suggesting that downregulation of PPAR-γ in the hippocampus by SEV might contribute to exaggerated neuroinflammation and consequently cognitive decline by increasing the sensitivity and susceptibility to CIH insult.

Experimental studies in animals have reported that systemic treatment with PIO attenuates brain microglial activation and neuroinflammation, improves neuronal survival, and prevents cognitive impairment in many inflammatory central nervous system disorders, such as chronic stress (32), alcohol-induced neuronal damage (31), traumatic brain injury (35) and forebrain ischemia/reperfusion injury (36). In the present study, systemic treatment with PIO, starting one day prior to SEV exposure, markedly increased PPAR-γ expression and activity in the hippocampus of CIH-SEV rats, which were associated with significant reductions in microglia activity and proinflammatory cytokine expression. Moreover, systemic treatment with PIO also improved cognitive decline in CIH-SEV rats as indicated by decreased latency to find the hidden platform and increased the percent time spent in the target quadrant, suggesting that SEV exposure causes a decline in spatial learning and memory abilities under CIH conditions, which can be prevented by treatment with PPAR-γ agonist PIO. Of note, swimming speed was similar among the 4 experimental groups, indicating that no alteration in sensory-motor activity that would influence the Morris Water Maze performance was produced by either SEV exposure or PIO treatment. Importantly, systemic treatment with PIO also markedly increased PPAR-γ expression and activity in the hippocampus of CIH-CON rats but did not alter microglia activity and proinflammatory cytokine expression as well as cognitive function in these animals, suggesting that microglia activity and proinflammatory cytokine expression in the hippocampus of CIH-CON rats without SEV exposure are mediated by other mechanisms rather than PPAR-γ. However, SEV exposure reduced PPAR-γ expression and activity, which increased sensitivity to inflammatory stimuli, resulting in exaggerated inflammatory responses. Collectively, these results indicate that systemic treatment with PIO inhibits SEV exposure-induced exaggeration of microglia-mediated neuroinflammation and cognitive decline in CIH rats via upregulation hippocampal PPAR-γ. PPAR-γ can physically bind to NF-κB p65 to inhibit NF-κB activity (37,38), and SEV exposure has been reported to induce microglia activation and neuroinflammation through the NF-κB pathway (39,40). Thus, the salutary effects of PIO treatment in the brain of CIH-SEV rats may be explained by the ability of PPAR-γ to inhibit SEV-induced NF-κB activity.

It is worth noting that PPAR-α and PPAR-β, two other PPAR isotypes, are also expressed in the brain and have been shown to exert anti-inflammatory and neuroprotective actions (41). However, expression of PPAR-α and PPAR-β in the hippocampus was similar among the 4 groups, excluding the possibility that PIO treatment inhibited microglia-mediated neuroinflammation in CIH-SEV rats by modulation of PPAR-α and PPAR-β.

One limitation of the study should be acknowledged. In the present study, we measured PPAR-γ expression and activity in the hippocampus but did not examine any PPAR-γ downstream targets. Further studies are necessary to determine whether PPAR-γ downstream targets are involved in the beneficial effects of PIO treatment on SEV-induced cognitive dysfunction under CIH conditions and provide detailed mechanisms.

In summary, the present study demonstrated that treatment with PPAR-γ agonist PIO prevents anesthetic SEV-induced cognitive decline in CIH rats and that these beneficial effects are mediated by upregulation of PPAR-γ, which inhibits SEV-induced neuroinflammation in the hippocampus. These findings may provide new insight into the potential use of PIO for preventing anesthetic SEV-induced cognitive decline in surgical patients with obstructive sleep apnea.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contribution

XZ and JF designed the experiments and wrote the manuscript. XZ, NL, LLu, QL, LLi, PD, BY and DL performed the experiments, collected and analyzed the data. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

All experimental protocols were approved by the Animal Care and Use Committees of Shandong University and conducted in accordance with the guidelines of the Animal Care and Use Committee at Shandong University (Jinan, Shandong, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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