RESEARCH PAPER

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The protective role of circ_0016760 downregulation against sevoflurane-induced neurological impairment *via* modulating miR-145 expression in aged rats

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Sevoflurane can produce toxicity to the hippocampal tissues of brain, leading to nerve damage, causing learning and cognitive dysfunction. CircRNAs have been indicated to act as a key mediator in anesthetic neurotoxicity. This study focused on the effect of circ_0016760 on sevoflurane-induced neurological impairment. The GEO database (GSE147277) and RT-qPCR were used to predict and measure the circ_0016760 expression. The interaction of circ_0016760 and miR-145 was verified by dual-luciferase reporter assay. The CCK-8 assay, flow cytometry, ELISA, ROS kit, MWM test were carried out to measure the cell viability, apoptosis, inflammation indicators, ROS level, and cognitive and memory function of the rats. Sevoflurane exacerbated neurotoxicity by restraining cell viability, inducing cell apoptosis, neuroinflammation, and ROS generation, and causing learning and cognitive dysfunction. Circ_0016760 expression was increased in POCD patients from the GEO database and upregulated after sevoflurane exposure. miR-145 was a target miRNA of circ_0016760. Silencing of circ_0016760 weakened the effect of sevoflurane on cell viability, cell apoptosis, inflammation-related factors, oxidative stress, which could be reversed by miR-145 inhibitor. The animal experiments results showed that circ_0016760 played a protective effect on regulating the cognitive behavior of sevoflurane-treated aged rats, expression of inflammation cytokine, and oxidative stress factors through targeting miR-145 in sevoflurane-treated aged rat's hippocampal neurons. Our results revealed that silencing of circ_0016760 attenuated sevoflurane-induced hippocampal neuron injury by regulating miR-145 expression, which may provide potential insights into the treatment of sevoflurane-induced neurological impairment.

Key words: circ_0016760, cognitive dysfunction, anesthetics, neurotoxicity

INTRODUCTION

Sevoflurane is one of the main inhalation anesthetics commonly used in clinical practice, which has the characteristics of low fat-soluble solubility, weak damage to the airway, and fast awakening after anesthesia, so it is widely used in clinical (Huang et al., 2021). However, studies have shown that sevoflurane can produce certain toxicity to the hippocampal tissues of the brain, leading to nerve damage, and causing learning and cognitive dysfunction (Shen et al., 2022a). Although anesthesia greatly reduces the pain of patients undergoing surgery, anesthesia itself has the effect of temporarily stopping or suppressing brain function (Chen et al., 2022). Postoperative cognitive dysfunction (POCD) is one of the common postoperative complications in the elderly, which refers to cognitive decline, mental status changes, and memory decline in postoperative patients. Commonly used general anesthetics such as sevoflurane, isoflurane, and propofol are thought to be important causes of POCD (Guo et al., 2016). The detailed mechanism of anesthetics-induced neurological impairment remains unclear.

Non-coding RNAs (ncRNAs), including circRNAs, lncRNAs, and miRNAs, are involved in the regulation of

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various cellular activities, such as neurogenesis and differentiation (Dong et al., 2021; Du et al., 2022; Wu et al., 2022a). CircRNAs could regulate miRNAs expression to participate in the occurrence and progression of a variety of diseases, such as Alzheimer's disease (Akhter, 2018; Shen et al., 2022), POCD (Yang et al., 2022b), and tumors (Kristensen et al., 2022). We identified one upregulated circRNA (circ_0016760) from the GEO database (GSE147277), which investigated the differentially expressed circRNAs in the serum of POCD and non-POCD patients by a circRNA microarray. Circ_0016760 was upregulated in non-small cell lung cancer and involved in the regulation of tumor progression and chemoresistance by regulating miR-625-5p expression (Zhang et al., 2018; Zou et al., 2022). However, the role and mechanism of circ_0016760 on sevoflurane anesthetics-induced neurological impairment remain unclear. The aberrant expression of miR-145 was involved in numerous human diseases, including atherosclerosis (Zhang et al., 2022), myocardial infarction (Huangfu et al., 2020), coronary heart disease (Li et al., 2020), neuropathic pain (Shi et al., 2018), and cognitive impairment (Regueira et al., 2022). Our further bioinformatic analysis based on circBank and CircInteractome online databases proved that there are binding sites between circ_0016760 and miR-145-5p.

Therefore, we hypothesized that circ_0016760 may regulate anesthetics-induced neurological impairment by targeting miR-145-5p in cognitive dysfunction impairment. Herein, we focused on the effects and mechanisms of circ_0016760 and its sponge miR-145-5p on sevoflurane-induced neurological impairment using healthy elderly (20 months old) male SD rats and mouse hippocampal neuron HT22 cells.

METHODS

Bioinformatics analysis

The differentially expressed circRNAs data in POCD were obtained from the GEO database (GSE147277). Heatmap was conducted based on fold change ≥3, P<0.05. Then the downstream miRNAs of circRNA were searched using online Circular RNA Interactome (CircInteractome; https://circinteractome.nia.nih.gov/index.html) and circBank (http://www.circbank.cn/index.html).

Cell culture and treatment

Mouse hippocampal neuron HT22 cell line (BeNa Culture Collection, Beijing, China) was incubated in DMEM (Gibco, USA) supplemented with 10% FBS in a 5% CO_2 incubator at 37°C. For cell transfection treatment, the HT22 cells were seeded in 6-well plates and divided into different groups. The vectors of circ_0016760 siRNA (si-circRNA; 5'-GTCTGGCATGCAGAGGCAGAA-3'), siRNA negative control (si-NC; 5'-CGTCAACATGGCTTTCACC-3'), mimic NC (5'-UUUGUACUACACAAAAGUACUG-3'), miR-145 mimic (5'-GUCCAGUUUUCCCAGGAAUCCCU-3'), inhibitor NC (inhi-NC; 5'-CAGUACUUUUGUGUAGUACAAA-3'), and miR-145 inhibitor (inhi-miR-145; 5'-AGGGAUUCCUGGGAAAACUGGAC-3') were synthesized and obtained from GenePharma (Shanghai, China). Transfection or co-transfection was performed with the Lipofectamine 3000 reagent (Invitrogen, Carlsbad, USA) for 48 h. For sevoflurane (SEV) exposure treatment, a homemade anesthesia chamber was used with 4 h exposure to 2.5% sevoflurane (Guo et al., 2018; Liu et al., 2015).

RT-qPCR

The total RNA of each group was extracted according to the instruction of the Trizol kit (Invitrogen, CA, USA), and cDNA was synthesized by reverse transcription using the Primescript™ RT reagent kit (Takara). Then RT-PCR analysis was performed using an SYBR Premix Ex Taq™ (Takara). GAPDH/U6 was used as the internal control. The sequences of the primers used for RT-PCR are the following: circ_0016760, forward, 5'-CTCAGAAGCGCAAGAACCTC-3' and reverse, 5'-TGGGCTCCAGGTAGTAGGTG-3'; GAPDH, forward, 5'-TATGATGACATCAAGAAGGTGGT-3' and reverse, 5'-TGTAGCCAAATTCGTTGTCATAC-3'; miR-145 forward: 5'-ACACTCCAGCTGGGTCCCTAAGGACCCTTTT-3', reverse, 5'-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGCAGGTCAA-3'; U6-forward: 5'-CTCGCTTCGGCAGCACA-3', reverse, 5'-AACGATTCACGAATTTGCGT-3'. The relative gene expression was calculated with the $2^{-\Delta\Delta Ct}$ method.

Dual-luciferase reporter assay

The circ_0016760 wide type (circRNA-WT) with binding sites of miR-145 or circ_0016760 mutant (circRNA-MUT) was synthesized and cloned into pmirGLO vectors to conduct circRNA-WT or circRNA-MUT constructs. Then circRNA-WT or circRNA-MUT together with miR-145 mimic or mimic NC were co-transfected into HT22 cells with Lipofectamine 3000, separately. After 48 h of co-transfection, the luciferase activity was measured by the luciferase reporter assay system (Promega).

CCK-8 cell viability assay

The cell viability was evaluated using CCK-8 assay. HT22 cells (5×10^4 cells/well) were seeded in 96-well plates. Then, CCK-8 reagent (10 μl) was added to each well, and the cells were incubated for a further 1 h. Then the absorbance (450 nm) was detected with a microplate reader.

Cell apoptosis detection

To measure the cell apoptosis changes, AnnexinV-FITC/PI solution was successively added into a cell suspension and worked for 10 min. Flow cytometry was used to measure fluorescence intensity.

Animal grouping and treatment

All animal experiments were handled according to the Guidance of Southwest Medical University Animal Ethics Committee. Sixty healthy elderly (20 months old) male SD rats (Slack Laboratory Animal Co. Ltd, Shanghai, China), weight 500-600 g, were divided into 6 groups randomly after 1 week of adaptive feeding. The 6 groups include the untreated group (control), sevoflurane (SEV) group, circ_0016760 siRNA (si-circRNA) group, siRNA NC (si-NC) group, si-circ_0016760 + antagomiR NC (si-circRNA+antagomiR-NC) group, and si-circRNA+miR-145 antagomiR group. These reagent vectors were purchased from GenePharma (Shanghai, China) and injected into the rats' brains with Entranster. Except for the untreated group, other groups were further treated with 2.5% sevoflurane for 4 h after injection of vectors for one week, respectively (Liu et al., 2022). Then, the Morris water maze (MWM) test was performed. The rats in each group were killed by anesthesia, and the hippocampal tissues of the brain were taken from the severed head on ice.

MWM test

MWM test was used to determine the cognitive and memory function of the rats after the modeling was completed. The rats were placed in the water maze for adaptive training for 3 days (4 times/day). On the fourth day, the positioning cruise experiment was performed: the rats were entered into the water from the middle of the pool wall in four quadrants, and the time from launching to climbing on the platform was recorded. The average of the four image limits was taken as the escape latency of the rats. If the rats did not board the platform within 90 s, they were guided to the platform to rest for 10 s, and the escape incubation period was recorded as 90 s. After the positioning cruise, pull out of the platform, enter the water from the original entry points of the four quadrants towards the pool wall, and record the time and distance percentage of rats crossing the position of the platform in the four quadrants within 90 s.

Reactive oxygen species (ROS) measurement

HT22 cells were harvested after transfection and sevoflurane exposure. ROS of cells was detected using ROS Assay Kit (Beyotime, Shanghai, China). In addition, lactated hydrogenase (LDH) levels, malondialdehyde (MDA), and superoxide dismutase (SOD) activity of cells were detected using the corresponding assay kit following the instruction of the manufacturer.

Enzyme-linked immunosorbent assay (ELISA)

The concentration of TNF-α, IL-6, and IL-1β in cell culture supernatants and plasma was determined using an available enzyme-linked immunosorbent assay kit (ELISA; R&D, USA).

Statistical analysis

Data were denoted as mean ± SD, then were analyzed using GraphPad Prism 9.0 software (GraphPad, La Jolla, USA). Comparisons were analyzed with Student's t-test, one-way analysis of variance (ANOVA), or two-way ANOVA followed by an appropriate *post hoc* test. $P<0.05$ was identified as statistically significant.

RESULTS

Circ_0016760 expression was upregulated in sevoflurane-treated HT22 cells and targeted with miR-145

We initially screened the circRNAs that were specifically expressed in human patients with postoperative cognitive dysfunction from the GEO database. From the differentially expressed circRNAs, circ_0016760 was identified as an upregulated circRNA (Fig. 1A). Interestingly, circ_0016760 expression was observed to be increased in 2.5% sevoflurane exposure treated HT22 cells compared with untreated HT22 cells ($t8=6.371$, $P<0.001$; Fig. 1B). By using online Circular RNA Interactome

(CircInteractome) and circBank, 12 downstream miRNAs were obtained. Among these miRNAs, miR-145 has significantly decreased expression levels ($F_{(11,96)}$=7.418, P<0.001; Fig. 1C) and is the candidate miRNA with potential binding sites with circ_0016760 (Fig. 1D), which was chosen for further experiments. Dual-luciferase reporter assay confirmed the binding relationship between circ_0016760 and miR-145 ($F_{(4,40)}$=84.84, P<0.001; Fig. 1D). Furthermore, miR-145 levels were raised in circ_0016760 downregulated HT22 cells ($F_{(3,16)}$=93.82, P<0.001; Fig. 1E).

The influence of circ_0016760/miR-145 axis in sevoflurane-treated HT22 cells

The transfection efficiency results showed that miR-145 expression was decreased by sevoflurane treatment, while was upregulated in si-circ_0016760-transfected cells, as well as miR-145 inhibitor could decrease its expression ($F_{(5,24)}$=88.11, P<0.001; Fig. 2A). The cell viability of HT22 cells was reduced by 2.5% sevoflurane, silencing of circ_0016760 could alleviate the inhibiting cell viability caused by sevoflurane, while down-

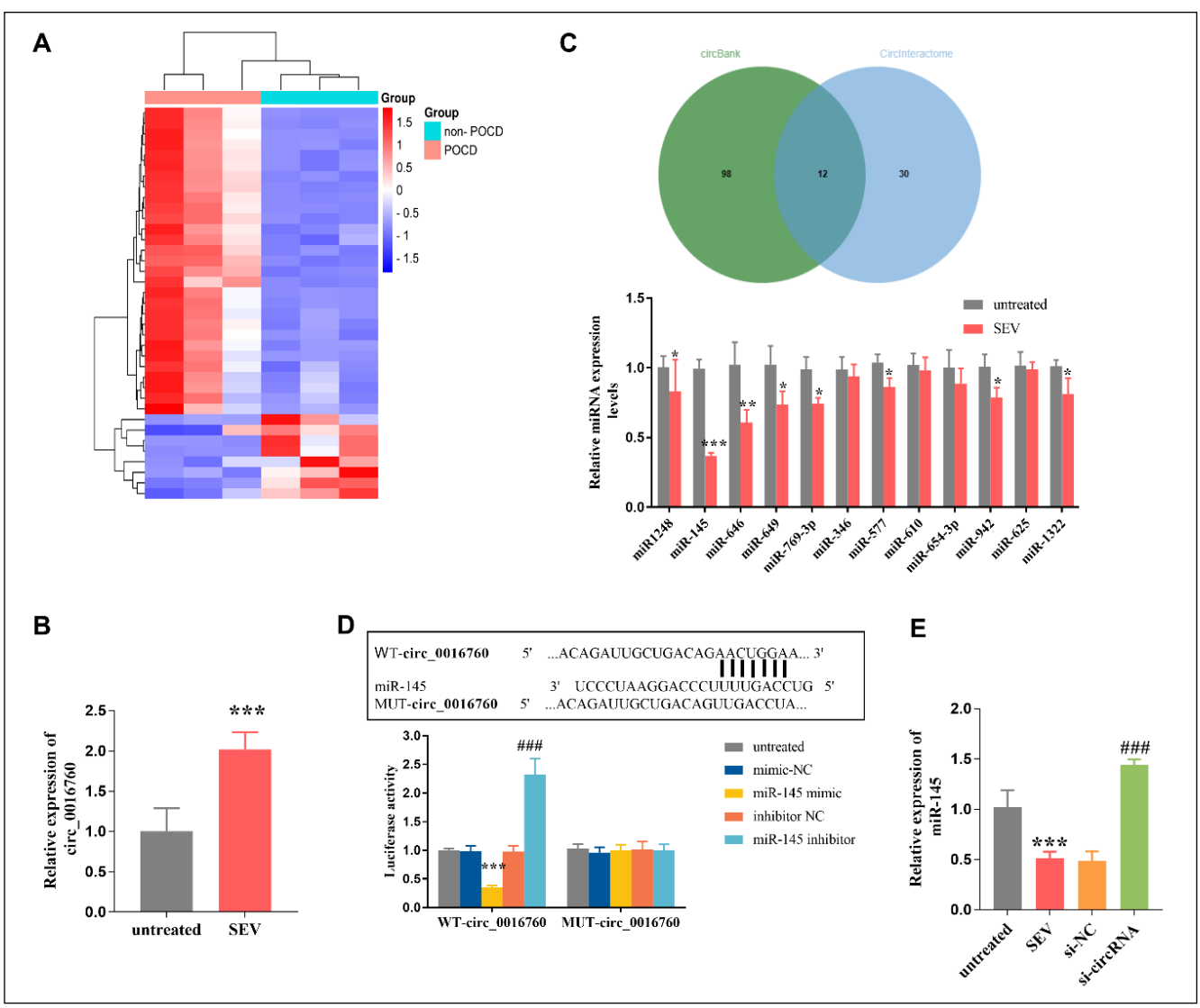

Fig. 1. The bioinformatic analysis of the binding interaction of circ_0016760 and miR-145. (A) The heatmap of differentially expressed circRNAs of the GSE147277 dataset from the GEO database. (B) Circ_0016760 was upregulated after sevoflurane treatment. ***P<0.001 *vs.* untreated. (C) CircBank and circInteractome databases were used to predict the potential binding miRNAs of circ_0016760. *P<0.05, **P<0.01, ***P<0.001 *vs.* untreated. (D) The binding sites between circ_0016760 and miR-145 were verified using a dual-luciferase reporter assay. ***P<0.001 *vs.* mimic NC; ###P<0.001 *vs.* inhibitor NC. (E) MiR-145 expression was decreased by sevoflurane treatment and upregulated after si-circ_0016760 transfection. ***P<0.001 *vs.* untreated. ###P<0.001 *vs.* SEV.

regulation of miR-145 diminished the increased viability caused by si-circ_0016760 ($F_{(15,96)}$=11.76, P<0.001; Fig. 2B). The cell apoptosis was enhanced after treating with sevoflurane, while was reversed by circ_0016760 knockdown, and decreased miR-145 expression diminished the effect of si-circ_0016760 ($F_{(5,24)}$=25.89, P<0.001; Fig. 2C). Additionally, the same trend with apoptosis change was observed in TNF-α, IL-6, and IL-1β levels ($F_{(10,72)}$=1.179; Fig. 2D), the main effects in a two-way analysis of variance are significant (P<0.001), but the interaction is not significant. As shown in Fig. 2E-2G, a similar change was observed in ROS ($F_{(5,24)}$=225.5, P<0.001; Fig. 2E), LDH ($F_{(5,24)}$=148.7, P<0.001; Fig. 2F), and MDA levels ($F_{(5,24)}$=2.15, P<0.001; Fig. 2G), while an opposite change was observed in SOD levels ($F_{(5,24)}$=35.02, P<0.001; Fig. 2H).

The influence of circ_0016760/miR-145 axis on the learning and remembering function in the aged rat model

As displayed in Fig. 3A, circ_0016760 expression was increased after sevoflurane treatment, while was decreased by si-circ_0016760 transfection ($F_{(3,16)}$=76.38, P<0.001). Fig. 3B showed that miR-145 expression was raised in hippocampal tissues inserted with si-circ_0016760, but could be inhibited by sevoflurane treatment and miR-145 antagomir ($F_{(5,24)}$=35.81, P<0.001). After sevoflurane management, the escape latency was increased ($F_{(25,144)}$=3.887, P<0.001), and the distance in the target quadrant ($F_{(5,24)}$=29.53, P<0.001) and the swimming time in the target quadrant ($F_{(5,24)}$=116.6, P<0.001) of aged rats was decreased (Fig. 3C-3E). The silencing of circ_0016760 increased escape latency, decreased percentage of distance, and swimming time in the target quadrant caused by sevoflurane treatment (Fig. 3C-3E). However, miR-145 inhibition eliminated the protective effects of si-circ_0016760 on cognition (Fig. 3C-3E).

The influence of circ_0016760/miR-145 axis on the sevoflurane-induced neurological inflammation in aged rats

ELISA assay results indicated that TNF-α, IL-6, and IL-1β levels were increased after sevoflurane treatment, the injection of si-circ_0016760 constrained the increased TNF-α, IL-6, and IL-1β levels induced by sevoflurane, while injection of si-circ_0016760 and miR-145

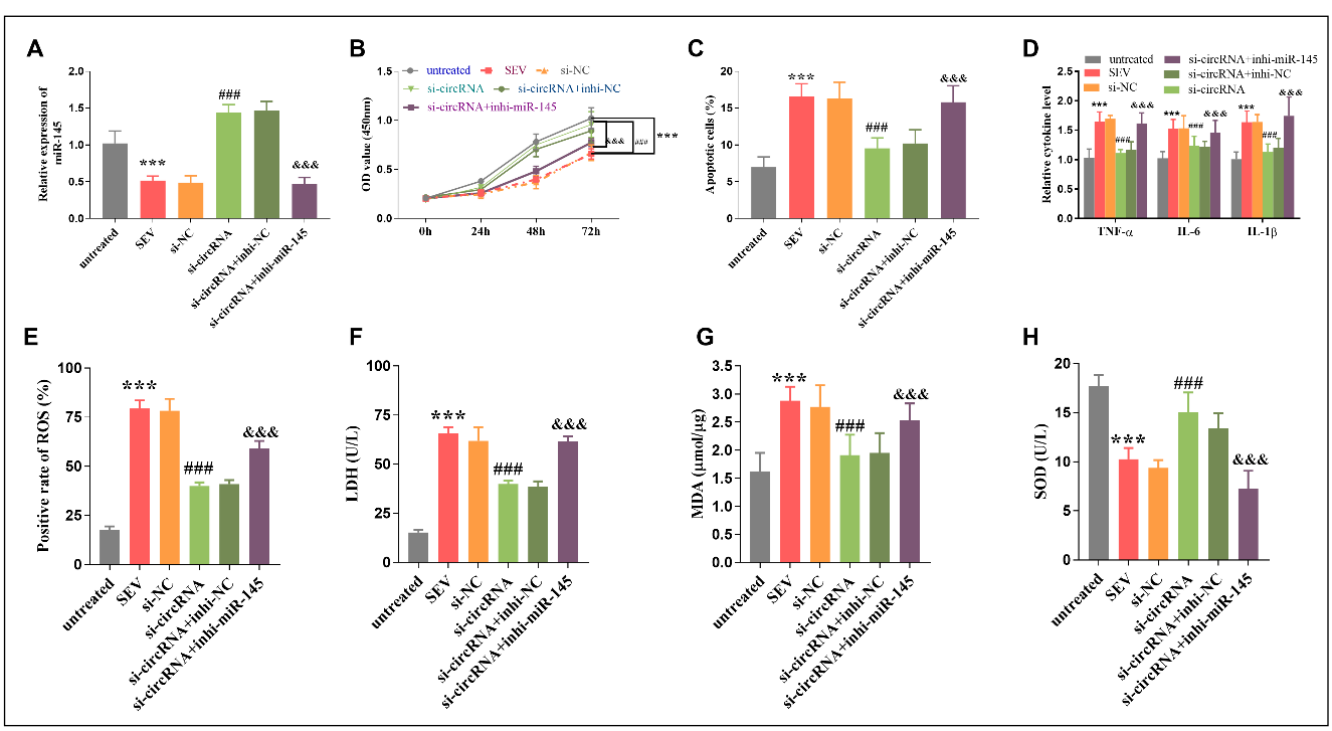

Fig. 2. The effects of circ_0016760/miR-145 axis in sevoflurane-treated HT22 cells. (A) RT-qPCR detected the miR-145 expression in different treatment groups. (B) CCK-8 assay measured the cell viability in different groups. (C) The apoptosis rate of HT22 cells was measured. (D) ELISA assay measured the changes in neurological inflammation factors. The oxidative stress indicator levels were detected in HT22 cells, including ROS (E), LDH (F), MDA (G), and SOD (H). ***P<0.001 *vs.* control, ###P<0.001 *vs.* SEV, &&&P<0.001 *vs.* si-circRNA+antagomir NC.

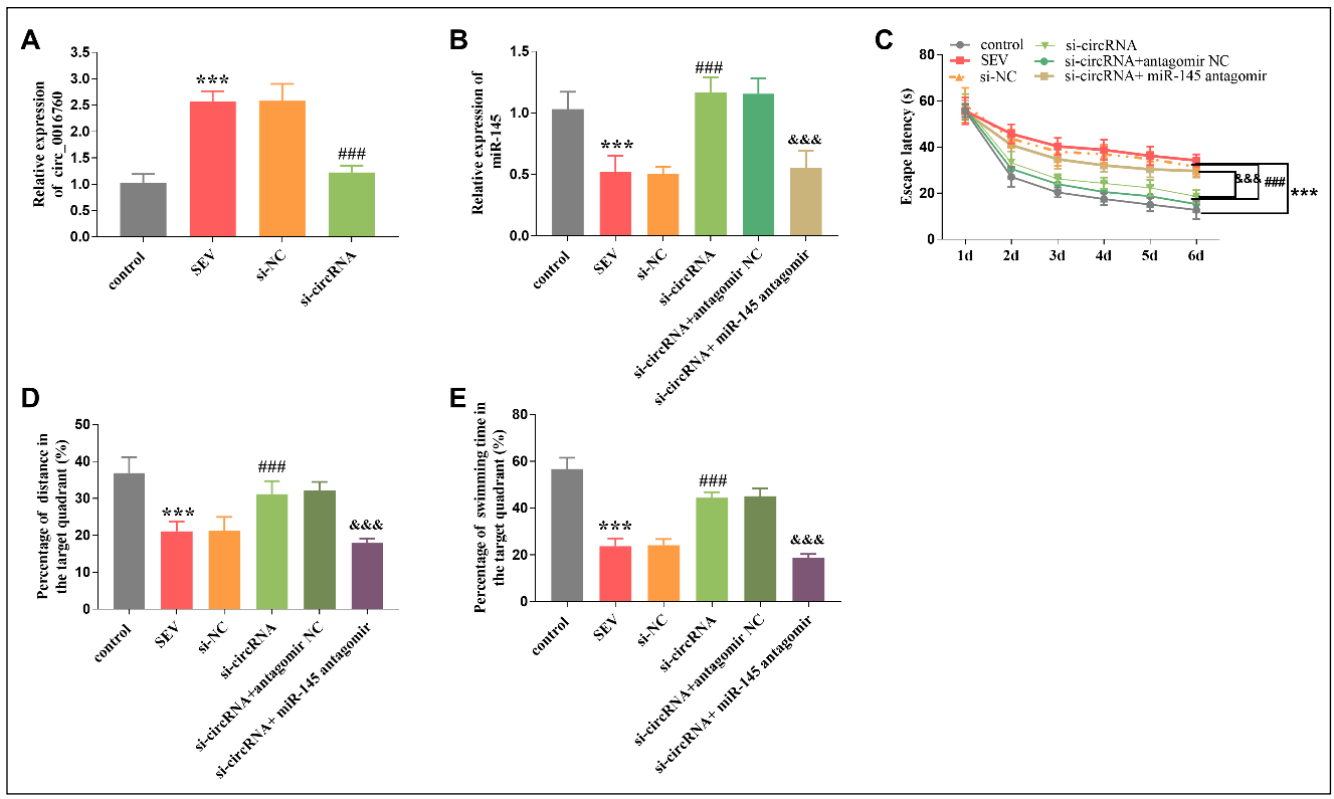

Fig. 3. The protective effect of silencing of circ_0016760 on the learning and remember function in the aged rat model. (A) RT-qPCR measured the relative expression of circ_0016760 in different groups. (B) RT-qPCR detected the relative expression of miR-145. (C-E) The cognitive function changes were detected in aged rats. ***P<0.001 *vs.* control, $^{\#\#\#}P$<0.001 *vs.* SEV, $^{\&\&\&}P$<0.001 *vs.* si-circRNA+antagomir NC.

antagomir eliminate the influence of si-circ_0016760 ($F_{(10, 72)}$=2.514, P<0.001; Fig. 4A).

As shown in Fig. 4B-4E, sevoflurane stimulates oxidative stress through accelerating positive ROS rate ($F_{(5,24)}$=65.37, P<0.001; Fig. 4B), LDH levels ($F_{(5,24)}$=75.70, P<0.001; Fig. 4C), MDA secretion ($F_{(5,24)}$=33.93, P<0.001; Fig. 4D), and decreasing SOD concentration ($F_{(5,24)}$=15.92, P<0.001; Fig. 4E), while silencing of circ_0016760 eliminated the effect of sevoflurane on oxidative stress. On the other hand, the knockdown of miR-145 abolished the protective effect of si-circ_0016760 (Figs. 4B-4E).

DISCUSSION

In this study, we investigated the influence of circ_0016760 on sevoflurane-induced cognitive impairment in aged rats and HT22 cells and explored the potential mechanism. The circ_0016760 was identified from the GSE147277 dataset with high expression in POCD elderly patients. Herein, circ_0016760 expression was upregulated in sevoflurane-induced cognitive impairment rat tissues and sevoflurane-treated HT22 cells. Silencing of circ_0016760 may protect the sevoflurane-induced learning and memory impairment in aged rats and suppress neurological inflammation and viabilities by regulating miR-145 expression.

The administration of gaseous, volatile anesthetics (such as isoflurane, desflurane, and sevoflurane) show neuroprotective effects, nevertheless, was associated with dose-dependent and exposure time-dependent neurodegenerative effects in the animal brain (Schifilliti et al., 2010). As an inhalation anesthetic widely used in recent years, sevoflurane has the advantages of hemodynamic stability and fast postoperative recovery compared with other inhalation anesthetics. Whereas, there were divergent views on the impact of sevoflurane on postoperative cognitive function. Some evidence revealed that sevoflurane has protective effects on the nerves in cerebral ischemia-reperfusion injury (Liang et al., 2021), ischemic brain injury (Wu et al., 2022b), and ischemic stroke (Cai et al., 2021). However, many studies indicated sevoflurane anesthesia can cause morphological and functional changes in the brain, which lead to cognitive impairment (Xiong et al., 2019; Tang et al., 2021; Liang et al., 2022). The mechanism underlying the effects of sevoflurane is not yet clear. NcRNAs, including circRNAs, are frequently

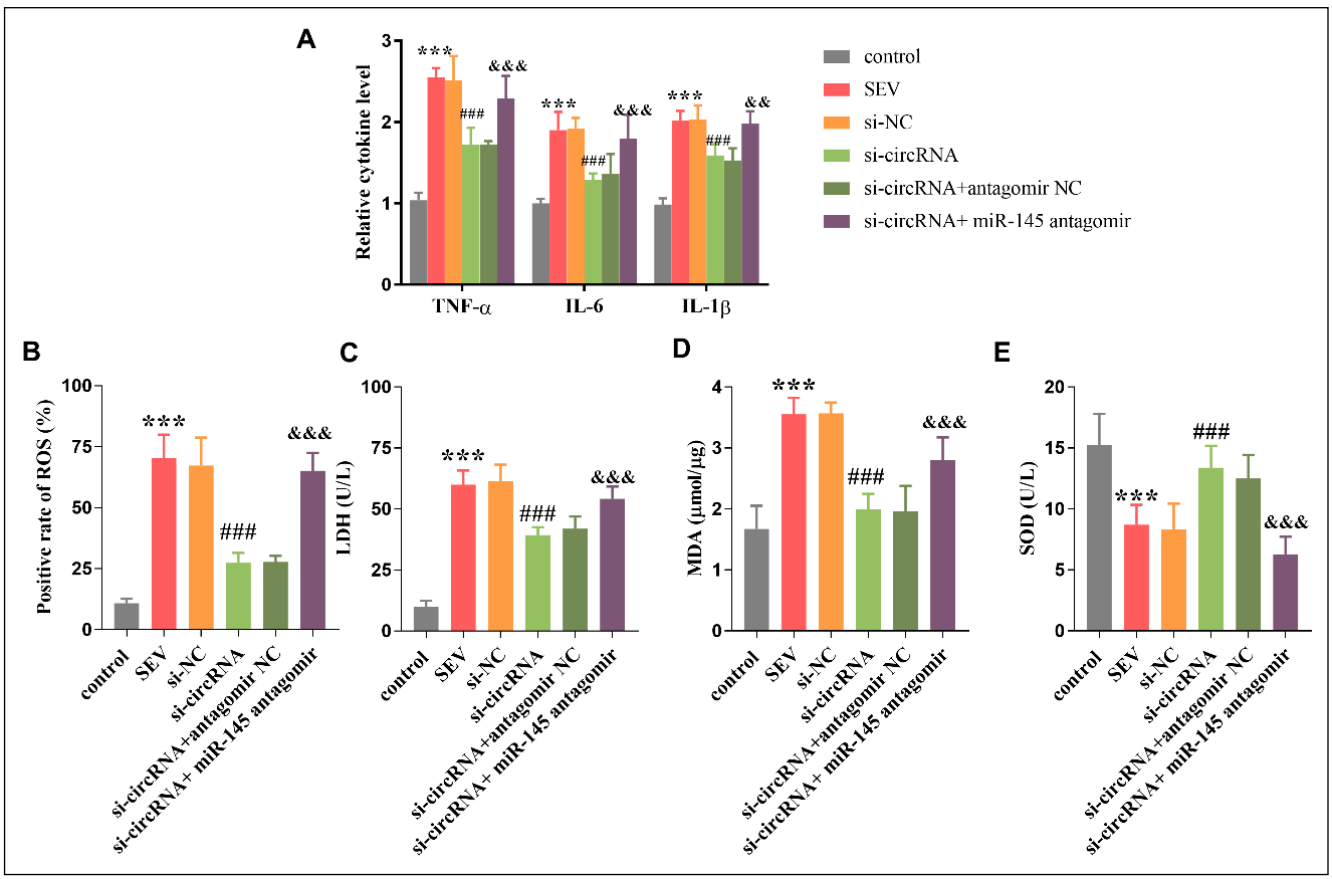

Fig. 4. The effect of circ_0016760/miR-145 axis on sevoflurane-induced neurological inflammation and oxidative stress in aged rat hippocampal neurons. (A) The relative cytokine levels in sevoflurane-treatment aged rat hippocampal neuron. The ROS (B), LDH (C), MDA (D), and SOD (E) levels were measured in neonatal-aged rat hippocampal neurons. ***P<0.001 *vs.* control, ###P<0.001 *vs.* SEV, &&&P<0.001 *vs.* si-circRNA+antagomir NC.

expressed in brain tissues and involved in neural development, suggesting that ncRNAs play key roles in diseases of the nervous system, such as Alzheimer's disease (Ma et al., 2020; Xu et al., 2020). For instance, circUBE3B contributed to sevoflurane-induced neuron injury by regulating miR-326 (Qian et al., 2023). These data revealed the crucial role of ncRNAs in the effects of sevoflurane-induced nervous injury. In this study, circ_0016760 was upregulated in POCD patients compared with non-POCD patients from the GEO database. Interestingly, circ_0016760 expression was upregulated in 2.5% sevoflurane-treated HT22 cells and sevoflurane-induced nervous injury hippocampal tissues of aged rats, suggesting that the abnormal expression of circ_0016760 may be involved in the regulation of sevoflurane-induced neurotoxicity.

Increasing studies revealed that the abnormal expression of circRNA participates in physiological processes, such as learning and memory, neuroplasticity, and cognitive deficits in aged animals (Zajaczkowski et al., 2021; Zhang et al., 2023). In this study, silencing of circ_0016760 played a protective effect on sevoflurane-induced neuron injury. The data indicated that sevoflurane damaged the HT22 cell viability and increased inflammation while circ_0016760 knockdown reversed the damaged influence of sevoflurane. Oxidative stress, as a pathogenetic factor in disease, could be caused by intoxication with narcotics and alcohol (Tufkova et al., 2020). Herein, sevoflurane caused oxidative stress by elevating ROS, LDH, and MDA leakage, and abrogating anti-oxidant SOD levels. The treatment with si-circ_0016760 afforded cytoprotective influence against oxidative stress caused by sevoflurane. CircRNA network by sponging miRNAs exerts functions in disease progression. This study verified that miR-145 was a direct target of circ_0016760. Additionally, inhibition of miR-145 could diminish the cytoprotective function of circ_0016760 silence in HT22 cells. The above results revealed that circ_0016760 knockdown could improve neurotoxicity mediated by sevoflurane through regulating miR-145 expression.

miR-145 is associated with pathological and physiological contexts in diseases, such as cardiovascular disease and atherosclerosis (Vacante et al., 2019; Chin et

al., 2021; Yang et al., 2021). A previous study pointed out that miR-145 was downregulated in sevoflurane-treated HT22 cells (Qi et al., 2019). Consistent with the previous study, the downregulation of miR-145 expression was observed in sevoflurane-treated HT22 cells. Moreover, the role of circ_0016760/miR-145 axis was observed in aged rats by affecting the escape latency, percentage of distance, and percentage of swimming time of the target quadrant, as well as inflammatory cytokine levels and oxidative stress in aged rats' hippocampal tissues. The results in both HT22 cells and aged rats revealed that silencing of circ_0016760 afforded cytoprotective influence against oxidative stress caused by sevoflurane through regulating miR-145 expression. These results revealed that silencing of circ_0016760 displayed a protective role in cognitive function through regulating miR-145 expression. A previous study indicated that miR-145 could prevent metabolic inflammatory disease, including atherosclerosis and type 2 diabetes, through multiple pathways (He et al., 2020). Circ_0010760 and miR-145 are closely related to PI3K/AKT signaling, MAPK signaling, Wnt/β-catenin signaling, TGFBR2 signaling, and notch signaling (Cao et al., 2019; Dinesh et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Chen et al., 2021). Circ_0016760 may participate in sevoflurane-induced neurological impairment through these above signaling pathways by regulating miR-145. However, the detailed mechanism of circ_0016760/miR-145 in sevoflurane-induced neurological impairment remains unclear and will be further investigated.

Here are some limitations. One limitation is that in vitro experiments only HT22 cells were used to explore the role of circ_0016760 in sevoflurane-induced neurological impairment. Other inhalation anesthesia, such as isoflurane, may also have neurological impairment. We only used sevoflurane to induce neurological impairment, which is another limitation.

CONCLUSION

In conclusion, our results indicated that silencing of circ_0016760 relieves the sevoflurane-induced cognitive impairment in aged rats by mediating miR-145 expression by alleviating neurological inflammation, oxidative stress, and apoptosis.

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