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Isoflurane induced cognitive impairment in aged rats through hippocampal calcineurin/NFAT signaling

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ABSTRACT

Calcineurin (CaN) over-activation constrains synaptic plasticity and memory formation. Upon CaN activation, NFAT imports into the nucleus and guides its downstream genes, which also affect neuronal and synaptic function. Aberrant CaN/NFAT signaling involves in neurotoxicity and cognitive impairment in neurological disorders such as Alzheimer's disease, but its role in postoperative cognitive dysfunction (POCD) remains uninvestigated. Inhaled anesthetic isoflurane facilitates the development of POCD, and the present study investigated the role of CaN/NFAT signaling in isoflurane induced cognitive impairment of aged rats, and the therapeutic effects of CaN inhibitor cyclosporine A (CsA). The results indicated that hippocampal CaN activity increased and peaked at 6 h after isoflurane exposure, and NFAT, especially NFATc4, imported into the nucleus following CaN activation. Furthermore, phamacological inhibition of CaN by CsA markedly attenuated isoflurane induced aberrant CaN/NFATc4 signaling in the hippocampus, and rescued relevant spatial learning and memory impairment of aged rats. Overall, the study suggests hippocampal CaN/NFAT signaling as the upstream mechanism of isoflurane induced cognitive impairment, and provides potential therapeutic target and possible treatment methods for POCD.

1. Introduction

Calcineurin (CaN) is a calcium/calmodulin-dependent serine/threonine protein kinase, which is sensitive to intracellular calcium level change. CaN is required for synaptic responses [1] and function [2], and could be a regulator for neuronal connectivity. Nuclear factor of activated T-cells (NFAT) imports into nucleus following CaN mediated dephosphorylation, and it also involves in axonal outgrowth [3], neuronal response [4], and synaptic development and plasticity [5]. While CaN/NFAT signaling is important for memory formation, its over-activation may also impair learning and memory. It has been reported that Alzheimer's disease (AD) associates with aberrant hippocampal CaN/NFAT signaling [6], and Aβ peptides could over-activate CaN activity in neurons [7]. Meanwhile, aberrant CaN/NFAT signaling is linked to pathologies such as synaptic dysfunction, astrocyte activation and neuronal death [8,9], and CaN inhibitor has been reported to attenuate relevant pathologies and improve cognition in AD model [10].

Postoperative cognitive dysfunction (POCD) is a major clinical issue in geriatric surgical patients [11]. It is self-limiting in most patients, but in some patients, it is long-term or even permanent [12]. POCD is associated with increased disability and early mortality [13]. Commonly used inhaled anesthestic isoflurane facilitates POCD and relevant neurotoxicity [14], but unfortunately, its upstream mechanism remains elusive. Isoflurane could induce over-activation of inositol 1,4,5-trisphosphate or ryanodine (IP3R) receptors on endoplasmic reticular (ER) membrane [15], and result in calcium leakage from ER [16]. Isoflurane could also increase bax/bcl-2 ratio and activate caspase 3 [17], which in turn cleaves IP3R and results in persistent calcium leakage [18]. These ER and mitochondria dependent pathways contribute to cytosolic calcium concentration elevation. Thus, isoflurane may lead to activation of CaN/NFAT signaling, but to our knowledge, the role of CaN/NFAT signaling in POCD remains uninvestigated.

Based on above-mentioned results and the similarity between AD and POCD, we hypothesize CaN/NFAT signaling involves in the development of POCD. And the present study aims to elucidate whether isoflurane activates hippocampal CaN/NFAT signaling and the involved NFAT isoform, furthermore, to evaluate the therapeutic effects of CaN inhibitor on isoflurane induced aberrant CaN/NFAT signaling and cognitive impairment.

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2. Materials and methods

2.1. Animals

Aged male Sprague–Dawley rats, 18 month old, weighing 550–600 g were used for the experiments. Before experiments, they were maintained on a standard housing condition with food and water ad libitum for 2 weeks.

2.2. Experiment protocols

The experimental protocols were approved by the Peking University Biomedical Ethics Committee Experimental Animal Ethics Branch (Approval No. LA201412). To investigate the effects of isoflurane exposure on CaN activity and NFAT nuclear import in the hippocampus, rats were randomly divided into isoflurane or control groups and received isoflurane (Baxter, Deerfield, IL, USA) or vehicle gas. CaN expression and activity were assessed with western blot and colorimetric analysis at 0, 3, 6, 12 and 24 h after isoflurane exposure ($n = 6$). Then NFATc2, c3 and c4 nuclear imports were observed at the most apparent CaN activation time point.

To investigate the role of hippocampal CaN/NFAT signaling in isoflurane induced cognitive dysfunction, rats were randomly divided into control, cyclosporin A (CsA, CaN inhibitor [19]), isoflurane or isoflurane + CsA groups. Rats in CsA and isoflurane + CsA groups received intraperitoneal injection of CsA (Abcam, Cambridge, UK) 7 mg/kg at 30 min before isoflurane exposure, and rats in other groups received normal saline. Then CaN activity and NFAT nuclear import were assessed, and hippocampus dependent spatial learning and memory function was assessed by Morris water maze test.

2.3. Isoflurane exposure

Isoflurane exposure was performed according to our previous study [20]. Briefly, rats received isoflurane, with 4 h treatment time in an anesthetic chamber. Isoflurane concentrations were monitored from gas outlet. SaO2, heart rate, blood pressure, and rectal temperature were also monitored. After exposure, rats received 100% oxygen until regaining consciousness. Isoflurane was well tolerated; meanwhile SaO2, heart rate, blood pressure and rectal temperature remained within physiological range. Rats in control and CsA groups just received vehicle gas.

2.4. Western blot

Western blot was performed to determine CaN expression in the hippocampus. Briefly, hippocampus and lysis buffer were homogenized and centrifuged, and total protein concentration of the supernatant was determined using BCA assay. Electrophoresis of protein lysates was performed on SDS–PAGE, and separated proteins were transferred to membranes and nonspecific binding sites were blocked. Then, membranes were incubated in anti-CaN antibody (1: 1000; Abcam, Cambridge, UK) or anti-β-actin antibody (1:10,000; Santa Cruz Biotechnology, Inc., Santa Cruz, CA), and incubated in fluorescently labeled secondary antibody (1:10,000; LI-COR, Lincoln, NE). Immunoreactivity was visualized by scanning membranes in an Odyssey infrared imaging system (LI-COR, Lincoln, NE). For densitometric analysis, data were calculated as a ratio of ChAT/actin.

2.5. Colorimetric assay

Colorimetric assay was performed to determine CaN activity in the hippocampus. Briefly, hippocampus and lysis buffer were homogenized and centrifuged, and protein concentration of the supernatant was determined using BCA assay. Protein lysates and calcineurin assay buffer were mixed, calcineurin substrate was added and reaction was proceeded for 10 min. Then green assay reagent was added and OD_{620nm} was read on a microplate reader (Thermo Scientific, Waltham, MA). OD_{620nm} data were converted into released phosphate amount, and calcineurin activity was calculated as a ratio of phosphate amount/reaction time.

2.6. Immunofluorescence

Immunofluorescence staining was performed to determine NFAT nuclear import in hippocampus. Briefly, hippocampus was fixed with 4% paraformaldehyde and cryoprotected with 30% sucrose. Cryosectioning was done with Leica cryostat (Leica, Deerfield, IL) at −20 °C. 10-μm-thick coronal sections were collected and incubated in anti-NFATc2, c3 or c4 antibody (1:100; Abcam, Cambridge, UK), and in FITC-conjugated secondary antibody (1:200; Santa Cruz Biotechnology, Inc., Santa Cruz, CA). Then nuclei were counterstained with DAPI (1:5000; Roche, Mannheim, Germany). Images were captured with Zeiss confocal fluorescence microscopy (Zeiss, Göttingen, Germany). As CA1 region of hippocampus plays an important role in memory formation [21], this region was analyzed.

2.7. Morris water maze

Spatial learning and memory was evaluated by Morris water maze. Place navigation test was performed 24 h after isoflurane exposure, during which rats received four training trials daily for 5 days, and during each trial, rats were placed in water facing the wall of maze at one of four equally spaced start positions. The time to locate submerged platform (escape latency, defined by cut-off time of 120 s) and the swim speed were recorded. Probe test (120 s) was performed 24 h after last trial, during which the platform was removed. The target zone transitions, target quadrant dwell time and swim path were recorded.

2.8. Statistical analysis

Statistical analysis was performed with Graphpad Prism 5.0 software. Data were expressed as means ± SD. One-way or two-way analysis of variance (ANOVA) was used to compare CaN expression and activity, and probe test results. Two-way repeated-measures ANOVA followed by post-hoc Bonferroni test was used to compare place navigation test results. Two-tailed test was employed in all comparisons. $P < 0.05$ was considered statistically significant.

3. Results

The expression and activity of CaN in the hippocampus of aged rats were examined over a 24 h period after isoflurane exposure, and the results show that CaN cleavage and the ratio of cleaved CaN to full length CaN increased significantly ($n = 6$). Specifically, it increased at 3 h after exposure, peaked at 6 h, and persisted in a relative high level at 12 and 24 h (Fig. 1A and B). Meanwhile, CaN activity increased after isoflurane exposure ($n = 6$). Similarly, it increased at 3 h after exposure, peaked at 6 h, and persisted in a relative high level at 12 and 24 h (Fig. 1C).

As CaN activation mediates NFAT nuclear import, and NFAT plays a role in synaptic plasticity and memory formation, NFAT nuclear import was observed. The observation point was selected at 6 h after isoflurane exposure based on the change of CaN activity. In the control condition, NFATc2, c3 and c4 were primarily distributed in the cytosol of pyramidal cell layer, CA1 region of hippocampus.

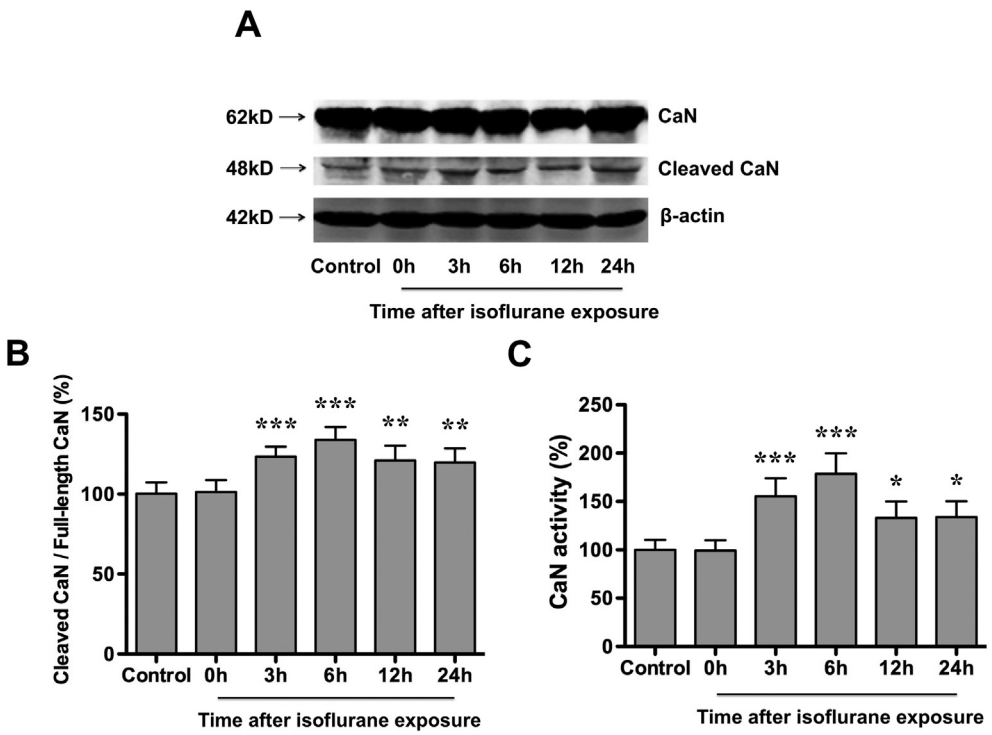

Fig. 1. Effect of 4 h isoflurane exposure on CaN cleavage and activity in the hippocampus of aged rats. (A and B) The hippocampal CaN cleavage increased significantly over time after isoflurane exposure, and peaked at 6 h (C) CaN activity also increased significantly over time after exposure, and peaked at 6 h. Data are expressed as means ± SD (n = 6). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs control group.

After isoflurane exposure, NFATc4 showed apparent nuclear distribution, but NFATc2 and c3 nuclear distributions were relative few (Fig. 2). These results indicate that isoflurane exposure could activate hippocampal calcineurin/NFAT signaling, especially through NFATc4 activation.

CsA, an inhibitor of CaN, has been reported to protect against brain injury [22]. In the present study, CsA significantly decreased isoflurane induced CaN cleavage (6 h after exposure), but CsA alone did not affect CaN cleavage (n = 6, Fig 3A and B). Meanwhile, CsA significantly decreased isoflurane induced CaN activation (6 h after exposure), and CsA alone also did not affect CaN activity (n = 6, Fig. 3C).

As NFATc4 showed apparent nuclear distribution after isoflurane exposure, the effect of CsA on NFATc4 nuclear import was observed. The results indicate that CsA attenuated isoflurane induced NFATc4 nuclear import, but CsA alone did not affect NFATc4 distribution, which remained primarily in the cytosol of pyramidal cell layer, CA1 region of hippocampus (Fig. 3D).

Finally, the effect of CsA on isoflurane induced cognitive impairment of aged rats was observed. Both group factor (treatment) and repeated factor (time) significantly affected escape latency ($P < 0.05$ and $P < 0.001$), and no interaction was found. The Bonferroni test shows that CsA significantly decreased isoflurane induced escape latency prolongation on the 4th and 5th days after exposure, but CsA alone did not affect escape latency (n = 12, Fig. 4A). There was no significant difference in the swim speed among four groups (Fig. 4B). In the probe test, CsA significantly increased both isoflurane induced target zone transitions and percentage of target quadrant dwell time reduction, but CsA alone affected neither target zone transitions nor percentage of target quadrant dwell time (Fig. 4C and D). Fig. 4E showed representive swim path of 4 groups in probe test. Taken together, these results show that CsA could rescue isoflurane induced cognitive impairment in aged rats through inhibiting aberrant hippocampal CaN/NFAT signaling.

4. Discussion

CaN is enriched in brain and could be activated by increased cytosolic calcium level of neurological disorders. Neuronal CaN has been reported to involve in synapse loss and dysfunction, neuronal vulnerability, neuroinflammation and neurodegeneration [23]. CaN constrains long-term potentiation (LTP) in the hippocampus, and over-expression of CaN inhibited transition from short-term to long-term memory [24]. CaN also blocks experience-dependent plasticity, a fundamental mechanism for learning and memory [25]. LTP is increased by genetic [26] or pharmacological CaN inhibition [27], on the contrary, long-term depression is blocked by CaN inhibition [28], which means CaN has dual effect in excitatory and inhibitory synapses. The present results show that isoflurane induced hippocampal CaN activation as well as memory impairment, which mean that CaN over-activation may play a role in the development of POCD.

CaN could dephosphorylate Ca^{2+} sensor/translocation domain of NFATc1-c4, resulting in NFAT nuclear import [29], and regulate synaptic function through this effect [30]. Basal activity of NFAT sits at intermediate level, and its reduction and elevation both affect synaptic function. In the hippocampus, synaptic activity regulates NFAT nuclear import, while NFAT and its downstream genes, such as IP3R1, also affect synaptic connections [31]. NFAT regulates presynaptic development and constrains long-term plasticity by dampening neuronal excitability [5]. NFAT over-expressing animals have more closed stable microtubule loops, and increasing NFAT activity in relevant neuronal circuits inhibits long-term behavioral adaptation [5].

During mild cognitive impairment, nuclear NFATc2 distribution increased in hippocampus, while nuclear NFATc4 distribution increased with intermediate to severe AD, and nuclear NFATc1 remained unchanged. In cerebellum, nuclear NFAT distributions

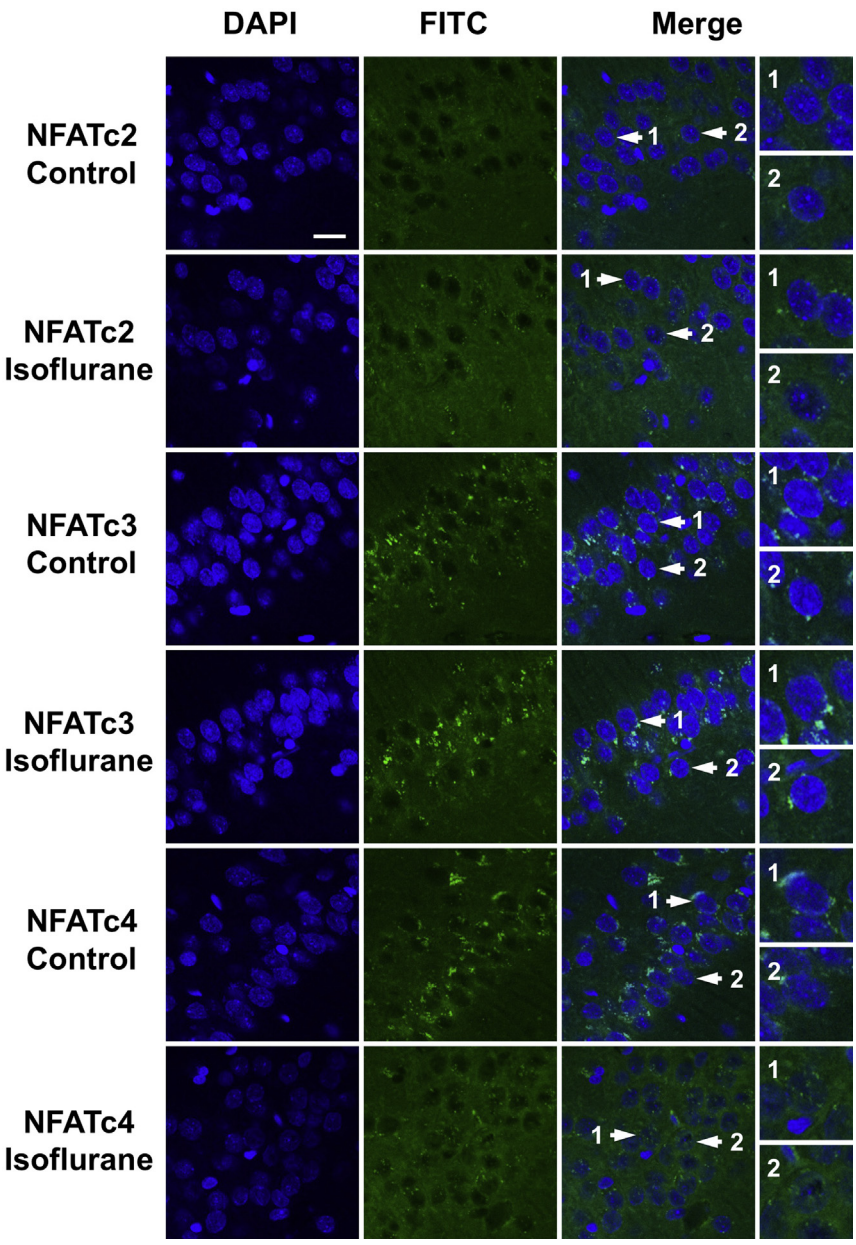

Fig. 2. Effect of 4 h isoflurane exposure on NFAT nuclear import in the hippocampus of aged rats. Confocal immunofluorescence images show double labeling for NFATc2-4 (FITC, green) and DAPI (blue) counter stain. In the control condition, NFATc2, c3 and c4 were primarily distributed in the cytosol of pyramidal cell layer, CA1 region of hippocampus. 6 h after isoflurane exposure, NFATc4 was distributed in both nucleus and cytosol, but NFATc2 and c3 nuclear distributions were relative few. In each panel, arrows point to the regions that present typical NFAT distribution, which are provided as high magnification images in the corresponding right panels. Magnification 400×, scale bar 20 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

were similar in different cognitive status, suggesting that NFAT involvement is restricted to vulnerable tissue [32]. In hippocampal neurons, elevations of calcium concentration rapidly induced NFATc3 nuclear import, and NFATc4 exhibited nuclear import only after prolonged (1–3 h) depolarization, which requiring coincident suppression of GSK3β [33], and isoflurane has been reported to inhibit GSK3β activation during brain injury [34]. We observed the nuclear imports of NFATc2, c3 and c4 in the hippocampus of aged rats, and found that 4 h isoflurane primarily induced NFATc4 nuclear import. As each NFAT isoform regulates unique transcriptional program, the results indicate that NFATc4 and its downstream genes involve in isoflurane induced synaptic dysfunction and development of POCD.

CsA is a specific CaN inhibitor. It could bind to cytosolic protein cyclophilin, and the complex of cyclosporin and cyclophilin inhibits calcineurin activity, then in step, prevents the dephosphorylation of NFAT and its nuclear import [35]. CsA crosses the blood–brain barrier (BBB) only after brain damage, such as brain ischemia [36]. We have found that isoflurane induced hippocampal BBB ultrastructure morphological damage and tight junction proteins occludin decrease, which resulted in BBB disruption and permeability increase [37]. Thus, it is possible that CsA inhibits isoflurane induced synaptic dysfunction by entering hippocampus through isoflurane induced BBB opening. The present results show that CsA attenuated isoflurane induced CaN activation and NFATc4 nuclear import, which means intraperitoneal CsA could be an effective inhibitor of aberrant

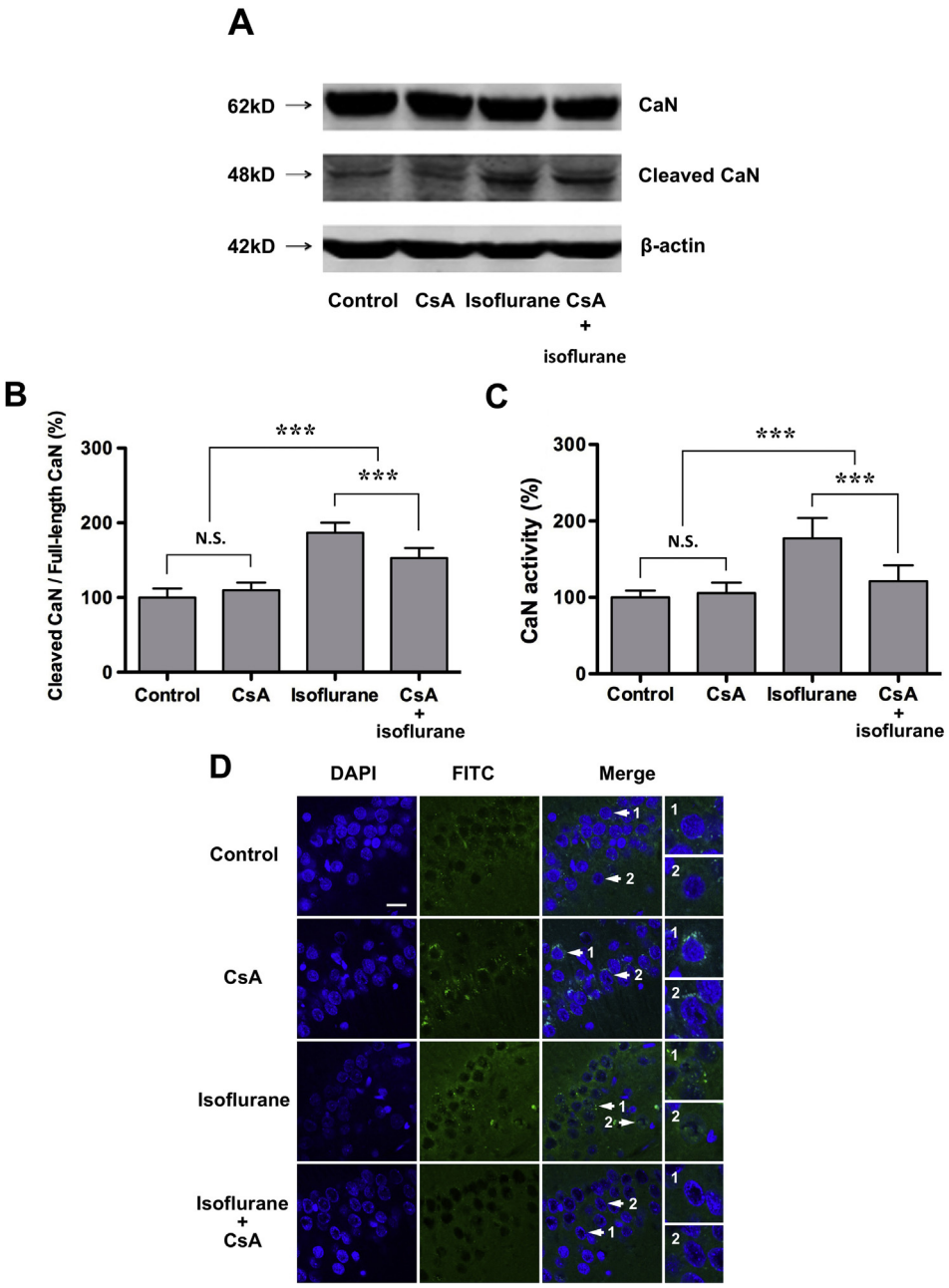

Fig. 3. CsA attenuated isoflurane exposure induced abberant CaN/NFAT signaling in the hippocampus of aged rats. CsA 7 mg/kg was injected intraperitoneally 30 min before exposure. (A and B) The hippocampal CaN cleavage increased significantly 6 h after isoflurane exposure. CsA attenuated isoflurane induced CaN cleavage, but CsA alone did not affect CaN cleavage. (C) CaN activity increased significantly after isoflurane exposure. CsA attenuated isoflurane induced CaN activation, but CsA alone did not affect CaN activity. (D) NFATc4 nuclear distribution increased after isoflurane exposure in the pyramidal cell layer, CA1 region of hippocampus. CsA attenuated isoflurane induced NFATc4 nuclear import, but CsA alone did not affect NFATc4 distribution. In each panel, arrows point to the regions that present typical NFAT distribution, which are provided as high magnification images in the corresponding right panels. Magnification 400×, scale bar 20 μm. Data are expressed as means ± SD (n = 6). $^{***}p < 0.001$.

CaN/NFAT signaling after isoflurane exposure. Meanwhile, CsA alone had no effect on spatial memory of rats, indicating that the effect of CsA is dependent on isoflurane induced BBB opening.

Isoflurane induces cognitive impairment in aged rats [36,38,39], and the present results show that CsA rescued isoflurane induced cognitive impairment. Considering the role of CaN/NFAT signaling in synaptic plasticity and memory formation, the results illustrate that CaN/NFAT signaling is an important upstream mechanism and potential therapeutic target for isoflurane induced cognitive impairment. APP transgenic mice display increased CaN activity in brain coincident with plaque formation and cognitive impairment, and could be treated by CaN inhibitor [40]. Aβ leads to aberrant CaN/NFAT activity in both neurons and astrocytes during the progression of AD [6]. Aberrant CN/NFAT also transcriptionally regulates β-site APPcleaving enzyme 1 (BACE-1), then BACE-1 promotes conversion of APP to Aβ, leading to the loss of neuronal function and viability [41]. We have found that isoflurane increased Aβ and related neurotoxicity in the hippocampus of aged rodents [14,20]. Thus, isoflurane may induce a vicious cycle of aberrant CaN/NFAT and Aβ increase, resulting in synaptic dysfunction and cognitive impairment, and CaN inhibitor could be an effective treatment to prevent this vicious cycle and isoflurane induced neurotoxicity.

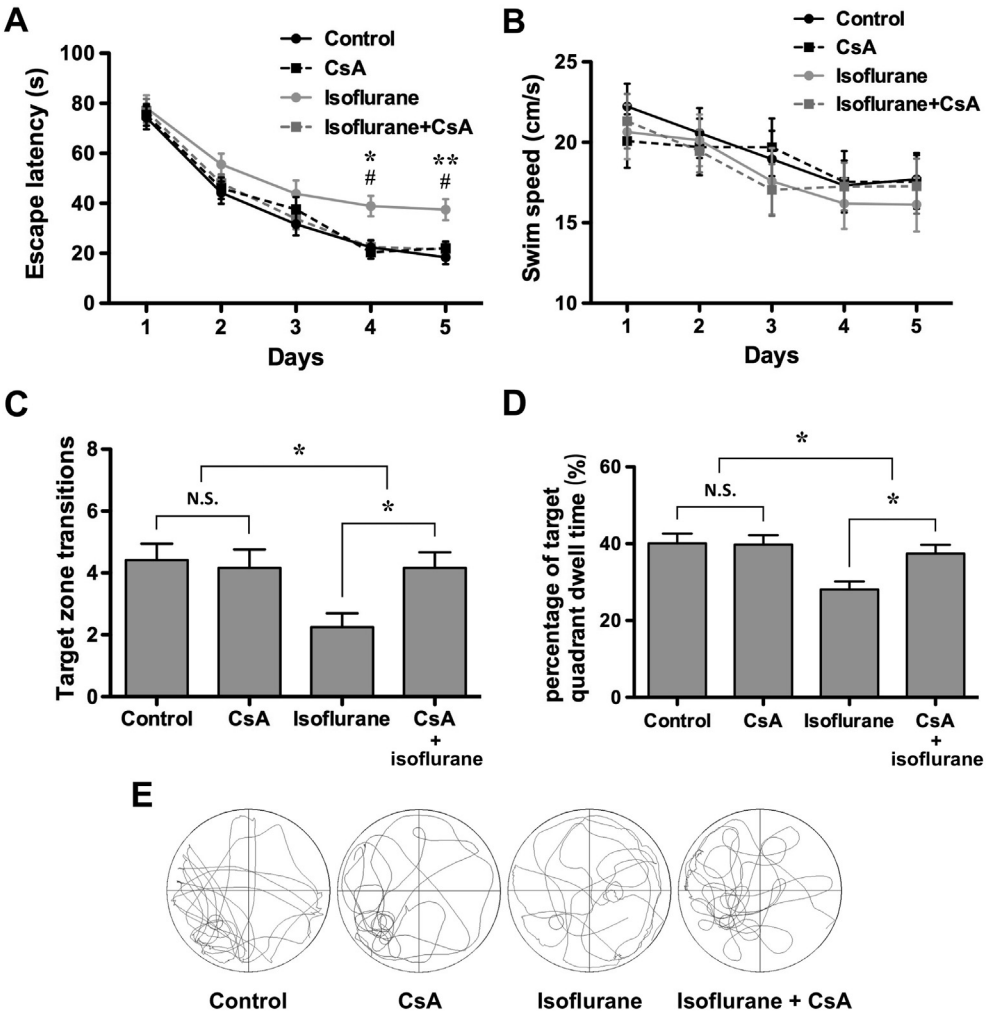

Fig. 4. CsA attenuated isoflurane exposure induced spatial memory impairment of aged rats. (A) Isoflurane increased escape latency as compared with control condition. CsA (7 mg/kg) attenuated isoflurane induced escape latency prolongation, but CsA alone did not affect escape latency ($^{*}p < 0.05$, $^{**}p < 0.01$ isoflurane group vs control group, $^{\#}p < 0.05$ isoflurane + CsA group vs isoflurane group). (B) Isoflurane and CsA did not affect swim speed. (C and D) Isoflurane decreased both target zone transition and percent of target quadrant dwell time as compared with control condition. CsA attenuated isoflurane induced target zone transition and percent of target quadrant dwell time decrease, but CsA alone did not affect them ($^{*}p < 0.05$). (E) Representive swim path of 4 groups in probe test. Data are expressed as means ± SEM (n = 12).

In conclusion, the present study indicates that isoflurane induces CaN activation and NFAT, especially NFATc4, nuclear import in the hippocampus. Furthermore, CsA attenuates isoflurane induced aberrant CaN/NFAT signaling, and rescues spatial learning and memory impairment of aged rats. These results reveal an important role of hippocampal CaN/NFAT signaling in inhaled anesthetic Isoflurane induced synaptic dysfunction and cognitive impairment, and provide potential therapeutic target and effective treatment methods for POCD.

Conflict of interest

We declare that we have no conflict of interest.

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Transparency document

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