Research Article

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TrkB Agonists Ameliorate Perioperative Neurocognitive Disorder

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ABSTRACT

This study investigated the therapeutic potential of tyrosine kinase B (TrkB) receptor activation against sevoflurane-induced perioperative neurocognitive disorder (PND) in aged male Sprague-Dawley (SD) rats (18 months old). Animals were exposed to 3% sevoflurane or control gas for 2 hours, with concomitant intraperitoneal (i.p.) administration of the TrkB agonist 7,8-dihydroxyflavone (7,8-DHF; 2.5 mg/kg) or antagonist ANA-12 (0.25 mg/kg). Sevoflurane exposure significantly impaired cognitive function, as evidenced by prolonged escape latency and reduced platform crossing times in the Morris water maze test. These deficits were associated with marked downregulation of hippocampal Cornu Ammonis 1 (CA1) expression of brain-derived neurotrophic factor (BDNF), TrkB, postsynaptic density protein 95 (PSD-95), and synaptophysin (SYP), together with reduced dendritic spine density. Treatment with 7,8-DHF effectively ameliorated cognitive impairment and restored synaptic protein expression and spine density. In contrast, ANA-12 exacerbated sevoflurane-induced deficits. These findings demonstrate that TrkB activation confers protection against PND by reversing sevoflurane-induced suppression of BDNF/TrkB signaling and synaptic integrity in the hippocampus.

Keywords: Sevoflurane; Perioperative Neurocognitive Disorder; Trkb Agonist; Synaptic; BDNF/Trkb Signaling

Abbreviations: TrkB: Tyrosine Kinase B; PND: Perioperative Neurocognitive Disorder; SD: Sprague-Dawley; CA1: Cornu Ammonis1; DHF: Dihydroxyflavone; BDNF: Brain-Derived Neurotrophic Factor; SYP: Synaptophysin; LTP: Long-Term Potentiation; AD: Alzheimer's Disease; HRP: Horseradish Peroxidase; ANOVA: Analysis of Variance; PSD: Postsynaptic Density; SYP: Synaptophysin; E-LTP: Early-Long-Term Potentiation; L-LTP: Late- Long-Term Potentiation; mBDNF: Mature BDNF; p75NTR: p75 Neurotrophin Receptor

Introduction

PND is a clinical syndrome encompassing postoperative delirium, cognitive dysfunction, memory deficits, and related impairments that may persist for weeks to months after surgery, predominantly affecting elderly patients. Epidemiological studies indicate that nearly 50% of older adults without baseline cognitive impairment exhibit measurable cognitive decline within the first postoperative month, with higher susceptibility observed among older males [1]. According to the World Health Organization's 2024 report "Ageing and Health in China," the proportion of adults aged over 60 in China is projected to double within the next 25 years. A significant number of these individuals already exhibit mild cognitive impairment, further elevating their risk of developing PND following surgical intervention [2-4].

Moreover, PND is associated with increased long-term risks of dementia, mortality, and other clinical complications [5,6], contributing substantially to healthcare burdens. Elucidating the etiology and mechanisms underlying PND is therefore critical for developing early diagnostic, preventive, and therapeutic strategies.

Long-term potentiation (LTP) in the CA1 subfield of the hippocampus represents a fundamental cellular mechanism underlying learning and memory [7,8].

It is classically divided into two distinct phases: an early, transient phase (E-LTP) and a late, persistent phase (L-LTP) [9]. E-LTP depends on calcium-mediated kinase activation and actin polymerization that induce dendritic spine enlargement [10-12], whereas L-LTP requires cAMP/PKA/CREB pathway-mediated transcription and de novo protein synthesis [13-15]. These phases provide the synaptic basis for short-term and long-term memory, respectively. Notably, L-LTP is robustly enhanced by BDNF, which is itself regulated by CREB. Upon binding to its receptor TrkB, BDNF activates downstream signaling cascades that critically promote synaptic plasticity [16-18]. This plasticity-characterized by dynamic changes in spine morphology (e.g., density, size) and synaptic protein expression (e.g., PSD-95, SYP)-forms the structural and functional foundation of memory encoding [19]. The BDNF-TrkB signaling axis thus serves as a critical link between transcriptional regulation and structural synaptic remodeling during memory consolidation. Dysregulation of this pathway contributes significantly to cognitive impairment in neurodegenerative disorders. For example, in models of Alzheimer's disease (AD), BDNF overexpression rescues synaptic loss and improves cognitive deficits [20].

Similarly, administration of TrkB agonists mimics BDNF-mediated neuroprotection, reversing spine atrophy and restoring memory function [21]. Collectively, these findings underscore the dual role of BDNF-TrkB signaling as both a key mechanistic bridge sustaining L-LTP and structural plasticity, and a promising therapeutic target for cognitive disorders. Building on the established role of BDNF-TrkB signaling in hippocampal synaptic plasticity, our previous work demonstrated significant downregulation ($p < 0.05$) of the cAMP/PKA/CREB pathway in sevoflurane-induced PND [22], establishing its pathogenic contribution to anesthesia-related cognitive decline. Given BDNF's critical function as a CREB-regulated neurotrophin in L-LTP mechanisms, we hypothesized that BDNF/TrkB signaling critically mediates PND pathogenesis. To test this, aged SD rats underwent 3% sevoflurane exposure (2 h) with concurrent pharmacological modulation using TrkB agonist 7,8-DHF (2.5 mg/kg, i.p.) or antagonist ANA-12 (0.25 mg/kg, i.p.). We conducted multimodal assessments including molecular profiling (BDNF via Western blot/RT-PCR, TrkB, PSD-95, and synaptophysin quantification), structural plasticity evaluation (Golgi staining of CA1 dendritic spine density), and functional cognitive testing (Morris water maze). This integrated approach directly addresses how BDNF-TrkB dysregulation drives sevoflurane-induced synaptic deficits, advancing targeted therapeutic strategies for PND. (Figure 1)

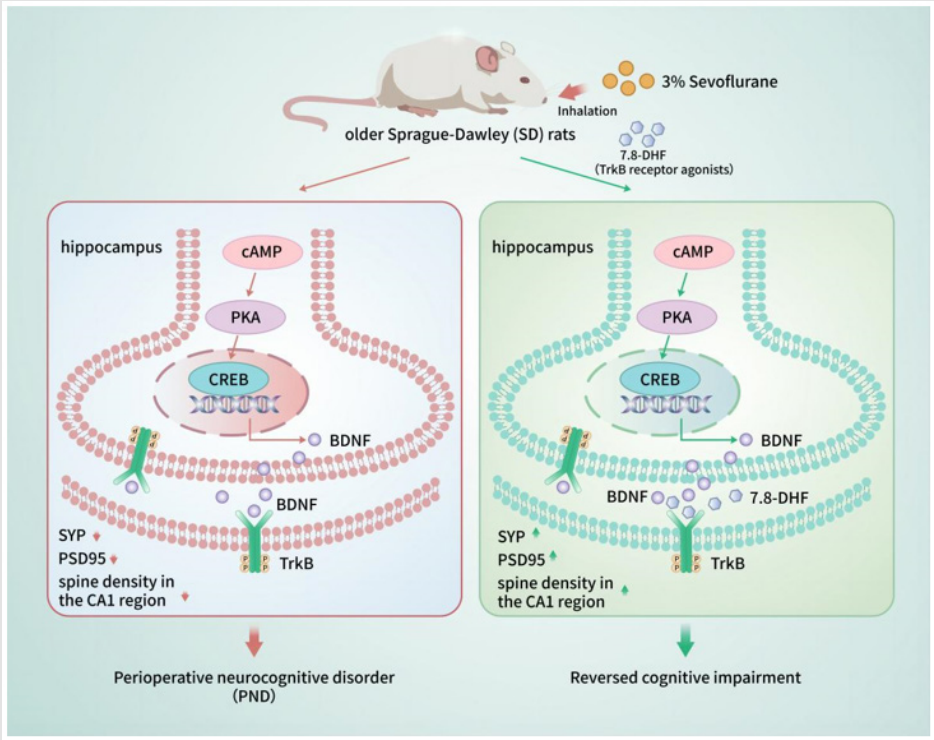

Figure 1: Experimental design flowchart elucidating the role of the BDNF-TrkB signaling pathway in sevoflurane-induced perioperative neurocognitive disorder (PND). The study utilized an aged SD rat model exposed to 3% sevoflurane (2 h) with concomitant pharmacological modulation. Multimodal validation was performed through molecular profiling, synaptic structural evaluation, and cognitive functional testing.

Materials and Methods

Experimental Cohorts and PND Modeling

Healthy 18-month-old male SD rats (600-800 g; specific pathogen-free) supplied by Xi'an Jiaotong University were acclimatized for 7 days under controlled conditions (22±1°C, 55 ±5% humidity, 12-h light/dark cycle) with ad libitum access to food and water, then randomly divided into four groups (n = 9/group):

1. Control (C): Sham gas exposure)
2. Sevoflurane (S): 2 h exposure to 3% sevoflurane (Hebei Pharmaceutical)
3. Agonist (S+A): Sevoflurane + 7,8-DHF (2.5 mg/kg, i.p.; MedChemExpress)
4. Antagonist (S+B): Sevoflurane + ANA-12 (0.25 mg/kg, i.p.; MedChemExpress).

This study received ethical approval from the Ethics Committee of Inner Mongolia Medical University (No: YKD202101139). For PND induction, groups S, S+A, and S+B were placed in a 37°Cinduction chamber (Xiagen Instruments) containing sodium phosphate for CO_2 absorption and exposed to 3% sevoflurane in 1:1 O_2 (2 L/min, 2 h) [23,24] via a Draeger anesthesia machine, with continuous gas monitoring (GE Healthcare; Shanghai Sources adsorber) and vital sign observation to prevent hypoxia, while controls received oxygen-only exposure; all animals recovered in home cages post-procedure.

Following successful PND validation via Morris water maze testing, rats received daily intraperitoneal injections for 7 consecutive days: S+A was administered 7,8-DHF (2.5 mg/kg in 5% PEG-300 + 2% Tween-80 + DMSO vehicle; Solarbio), S+B received ANA-12 (0.25 mg/kg in identical vehicle), and groups C and S were given vehicle solution alone, with dosing regimens based on established interspecies scaling protocols [25,26].

Morris Water Maze

Cognitive function was evaluated in a Morris water maze (1.6 m diameter; 24°C water) using the ANY-maze™ tracking system. Acquisition trials (4 trials/day×5 days) measured escape latency and swimming distance to a submerged platform (8 cm diameter). Probe tests (60 s platform-free swims) were conducted on Day 6 and post-intervention days 1, 3, and 7, quantifying platform crossing times and target quadrant dwell time. Animals failing to locate the platform within 60 s were guided to it and permitted 12 s of spatial orientation.

Tissue Collection and Processing

Hippocampal sampling occurred at 1,3 and 7days post-intervention (n=3/group/timepoint). After pentobarbital sodium anesthesia (100mg/kg, i.p.; Shanghai Yihe Biotechnology Co., Ltd.), rats underwent transcardial perfusion. Craniotomies were performed on ice-chilled pads, with hippocampi dissected within 2 min post-sacrifice. Tissues were divided: left hippocampi were fixed in 4% paraformaldehyde (24 h, 4°C) for histology, while right hippocampi were snap-frozen in liquid nitrogen for molecular analyses and stored at -80°C.

Golgi Staining

Following standard tissue processing (sampling, fixation, staining, dehydration, clearing, sectioning, counterstaining, and mounting) of rat left hippocampal tissues, histological sections were digitized using the PANNORAMIC® panoramic slide scanner to capture comprehensive tissue information. Within CaseViewer® software (v2.4), target regions were selected and visualized at 400× magnification. Dendritic spine quantification was performed on intact neurons within image centers using Image-Pro Plus® 6.0 software, measuring spines along 30 - 90 μm segments of secondary or tertiary dendritic branches. Spine density was calculated as spines per 10 μm of dendrite.

Western Blot

Following total protein extraction from hippocampal tissues and concentration determination by BCA assay, 5 μl of Laemmli reducing sample buffer was added to protein lysates. The mixture was heat-denatured at 95°C for 15 min and stored at -20°C. After electrophoresis (SDS-PAGE), membrane transfer, and blocking, membranes underwent sequential incubations with primary antibodies (overnight, 4°C) and horseradish peroxidase (HRP)-conjugated secondary antibodies (2 hr, 24°C). Chemiluminescent signals were captured on X-ray film, scanned, and analyzed using Adobe Photoshop and Alpha Ease FC software for band densitometry to quantify protein expression levels of BDNF, TrkB, SYP, and PSD-95.

Real-Time PCR

Total RNA isolated from hippocampal tissues underwent reverse transcription to cDNA for quantitative real-time PCR (qRT-PCR). the comparative CT method (ΔΔCT method) was applied using GAPDH as the endogenous reference gene to analyze the relative expression levels of target genes. The expression of BDNF, TrkB, SYP, and PSD-95 genes in hippocampal tissues was quantified.

Statistical Analysis

Statistical analyses were conducted using SPSS 26.0. Data are presented as mean ± standard deviation (s.d.). Intergroup comparisons utilized one-way analysis of variance (ANOVA), followed by LSD post hoc tests for multiple comparisons where indicated, while intragroup comparisons employed repeated-measures ANOVA. Statistical significance was defined as $p<0.05$. Graphical representations were generated using GraphPad Prism 7.0.

Results

Sevoflurane-Induced Cognitive Deficits in Aged Rats

Statistical analysis revealed that 18-month-old SD rats exposed to 3% sevoflurane for 2 hours (Groups S, S+A, and S+B) exhibited significantly increased escape latency ($P < 0.01$) and swimming distance ($P < 0.01$), representing approximate increases of 40%-60% compared to both Group C (naive controls) and their own pre-exposure baselines (Day 5 prior to modeling). Concurrently, these animals demonstrated reduced platform crossing frequency ($P < 0.05$), corresponding to decreases of 29%-32% relative to control levels (Figure 2). These results indicate substantial impairment in spatial learning and memory function following sevoflurane exposure.

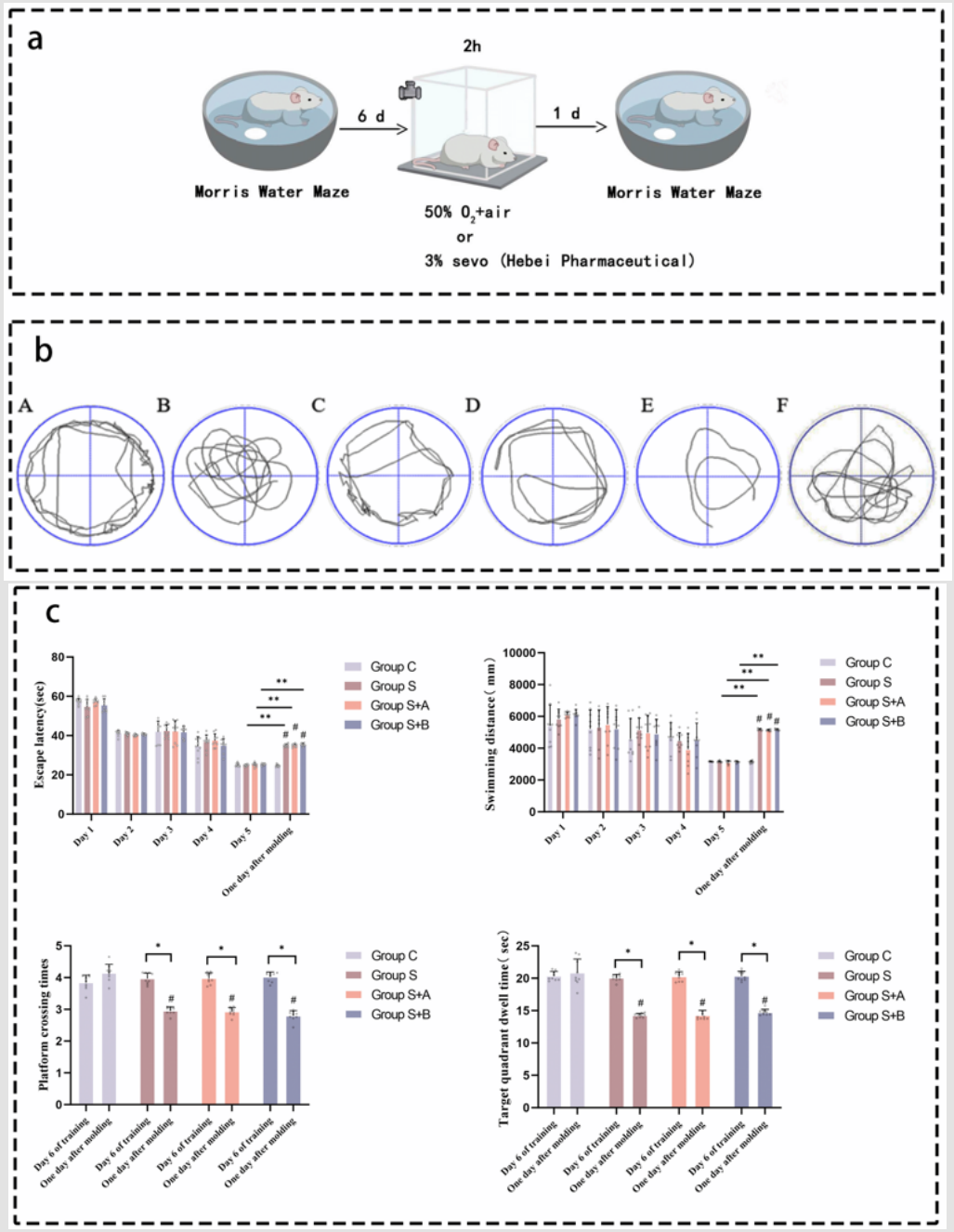

Figure 2: Cognitive impairment in 18-month-old SD rats following recurrent 3% sevoflurane inhalation 2 hours.

A. The method of PND rat model established.

B. Morris water maze behavioral trajectories during training and testing phases. A-E: Training trials (Days 1-5); F: Probe test (Day 6).

C. Intra-group comparison of Morris Water Maze behavioral performance across groups pre- and post-modeling. (**p < 0.01 vs. baseline; #p < 0.05 vs. Group C).

BDNF/TrkB-Mediated Impairment of Hippocampal Synaptic Plasticity Underlies Sevoflurane-Induced Postoperative Cognitive Dysfunction in Aged Rats

Following PND modeling, Group S (sevoflurane-exposed) rats demonstrated progressive behavioral recovery in Morris water maze testing: escape latency and swimming distance decreased across trials, while platform crossing times and target quadrant dwell time increased. Compared to Group C (naive controls), Group S exhibited significantly longer escape latencies ($P < 0.01$) and swimming distance ($P < 0.01$) on days 1 and 3, representing an approximate 40%-60% impairment in spatial learning efficiency, alongside reduced platform crossing times and shorter target quadrant dwell times, indicating a comparable deficit in memory retrieval and spatial preference (Figure 3). By day 7, these deficits resolved with no significant intergroup differences in Morris water maze parameters (Figure 3C). Western blot analysis revealed significantly reduced hippocampal expression of BDNF, TrkB, SYP, and PSD-95 in Group S versus Group C on days 1 and 3 ($P < 0.05$), corresponding to a reduction of approximately 48%-67% in BDNF, TrkB protein levels, 10%-20% in SYP, PSD-95 protein levels with expression levels normalizing to baseline in day 7 (Figure 3D).

RT-PCR analysis demonstrated transient downregulation of BDNF, TrkB, SYP, and PSD-95 mRNA in Group S hippocampus versus Group C on days 1 and 3 ($P < 0.05$), reflecting a decrease of roughly 60% in BDNF, TrkB transcript abundance, 30%-40% in SYP, PSD-95 transcript abundancewith expression levels normalizing to baseline in day 7 (Figure 3D). Golgi staining revealed significantly reduced dendritic spine density in hippocampal CA1 neurons of Group S versus Group C on days 1 and 3 ($P < 0.05$), reflecting an approximate 10%-20% decrease in synaptic connectivity, with full normalization to baseline levels by day 7 (Figure 3B).

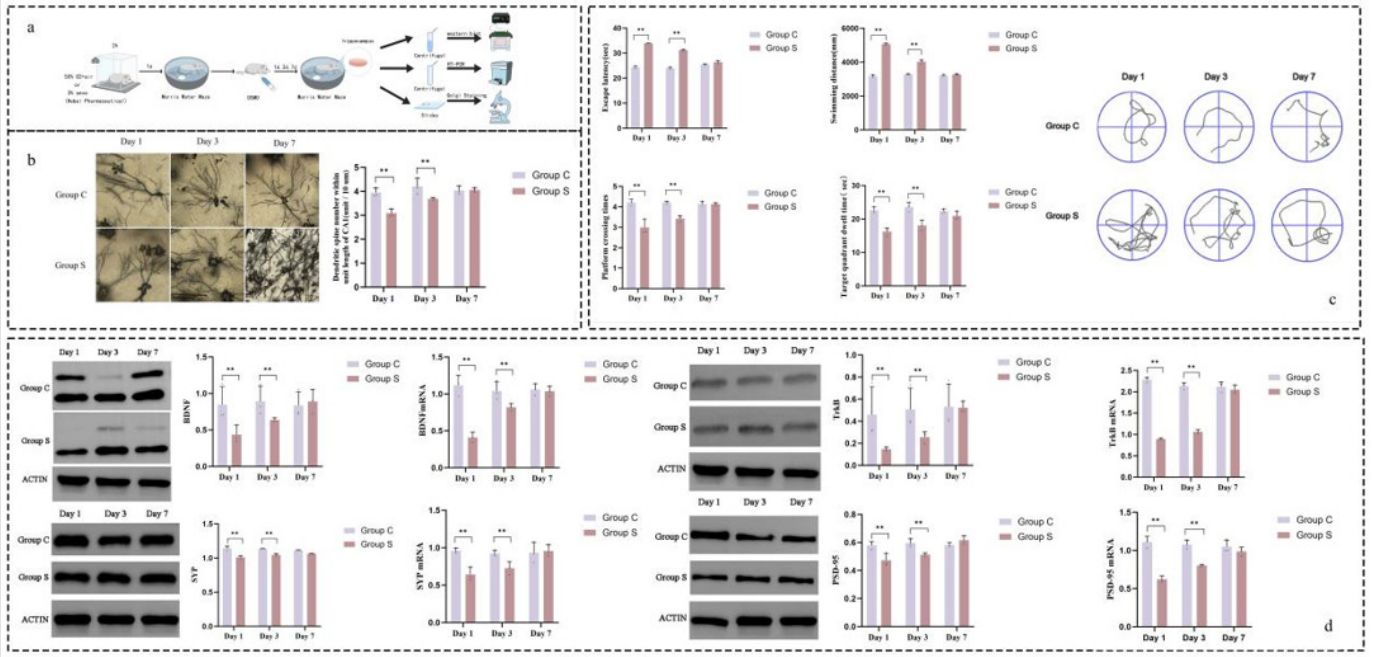

Figure 3: BDNF/TrkB-Mediated Impairment of Hippocampal Synaptic Plasticity Underlies Sevoflurane-Induced Postoperative Cognitive Dysfunction in Aged Rats (*$p < 0.05$; **$p < 0.01$).

A. Experimental design timeline.

B. Dendritic spine density in hippocampal CA1 neurons (Group S vs. Group C; mean ± s.d., n = 3 biologically independent samples).

C. Morris water maze behavioral metrics: escape latency, swimming distance, platform crossing times, and target quadrant dwell time (mean ± s.d., n = 3 rats/group).

D. Molecular dynamics: Hippocampal protein (BDNF, TrkB, SYP, PSD-95) and corresponding mRNA expression levels at post-intervention days 1, 3, and 7 (mean ± s.d., n = 3 independent experiments).

TrkB Agonist 7,8-DHF Rescues Sevoflurane-Induced Cognitive Deficits Through Hippocampal Synaptic Plasticity Modulation

Pharmacological interventions produced time-dependent behavioral modulation in Morris water maze performance. Group S+A exhibited progressive reductions in swimming distance and escape latency throughout the intervention period, representing an approximate 10%-27% improvement relative to Group S, concurrent with increased platform crossing times and target quadrant dwell time relative to Group S ($P < 0.05$). Conversely, Group S+B demonstrated similar decreases in swimming distance and escape latency but showed reduced platform crossing times and shorter dwell times, reflecting an additional 15%-55% deficit in memory retrieval. Compared to naive controls (Group C), Group S+A displayed significantly longer path lengths ($P < 0.05$), extended escape latencies ($P < 0.05$), fewer platform crossing times, and diminished dwell times during postintervention days 1 and 3 (Figure 4). Group S+B, however, maintained shorter swimming distances and escape latencies yet exhibited substantially reduced platform crossing times and dwell time across all timepoints (days 1, 3, 7) (Figure 4C).

Western blot analysis revealed time-dependent molecular changes in hippocampal tissue. Both Groups S+A and S+B exhibited progressive increases in BDNF and TrkB protein expression post-modeling, while SYP and PSD-95 demonstrated divergent results: SYP and PSD-95 increased progressively in Group S+A but decreased in Group S+B with extended intervention. Compared to Group C, BDNF and TrkB expression was significantly reduced in both intervention groups at post-intervention days 1 and 3 ($P < 0.05$), but normalized to control levels by day 7. Conversely, SYP and PSD-95 expression in Group S+A showed significant elevation at days 3 and 7 ($P < 0.05$), indicating a 8%-40% increase in synaptic protein levels, whereas Group S+B maintained reduced levels at all timepoints ($P < 0.05$), representing a progressive 15%-52% deficit. When benchmarked against Group S, SYP and PSD-95 expression was significantly elevated in Group S+A ($P < 0.05$) but substantially reduced in Group S+B (maximum reduction at day 7, $P < 0.05$), with intergroup comparisons confirming significantly lower SYP and PSD-95 levels in Group S+B versus S+A across all timepoints ($P < 0.05$) (Figure 4D).

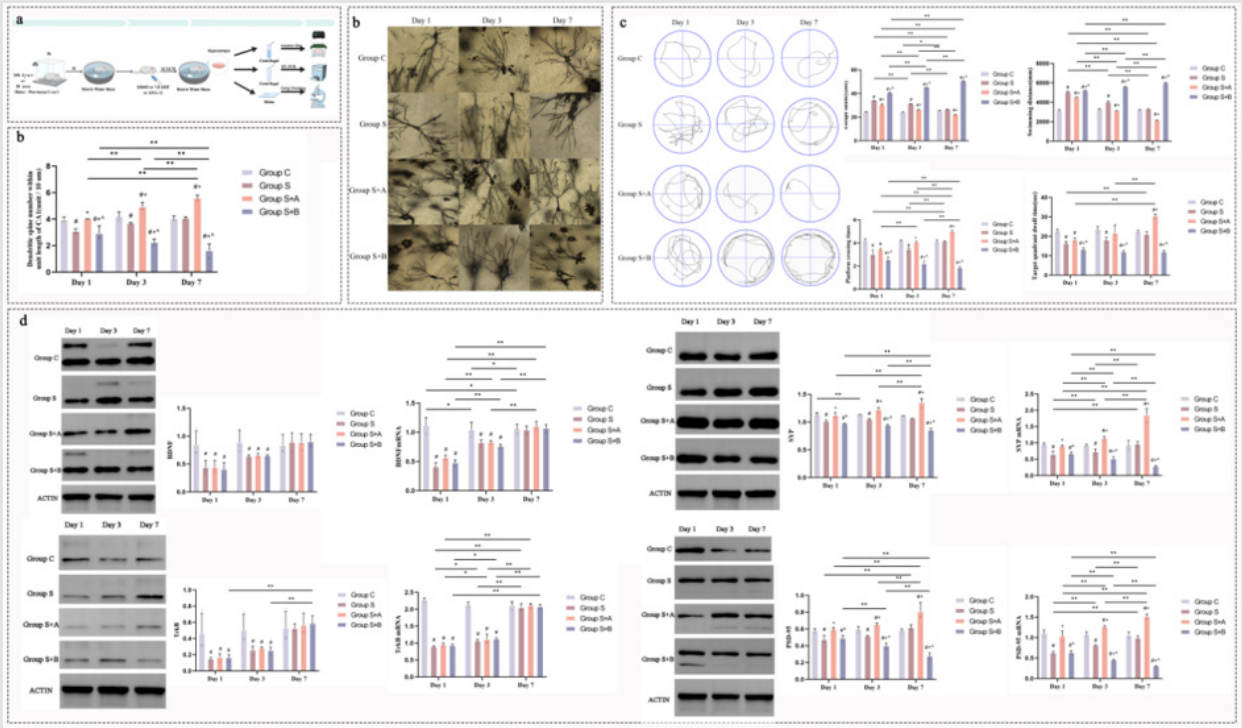

Figure 4: 7,8-DHF Infusion Modulates Hippocampal Synaptic Plasticity and Reverses Sevoflurane-Induced Cognitive Deficits (*$p < 0.05$; **$p < 0.01$; vs. Group C, #$p < 0.05$; vs. Group S, +$p < 0.05$; vs. Group S+A, ^$p < 0.05$).

A. Experimental design timeline.

B. Dendritic spine density in hippocampal CA1 neurons (spines/10 μm; mean ± s.d., n = 3 biologically independent samples; 400× magnification).

C. Morris water maze behavioral metrics: Representative swimming trajectories and quantitative analysis of escape latency, swimming distance, platform crossing times, and target quadrant dwell time (mean ± s.d., n = 3 rats/group).

D. Relative expression of BDNF, TrkB, PSD-95, and SYP in hippocampal lysates (mean ± s.d., n = 3 independent experiments).

RT-PCR analysis revealed corresponding mRNA dynamics in response to pharmacological interventions. Both Groups S+A and S+B exhibited progressive upregulation of BDNF and TrkB transcripts following modeling. However, significant downregulation was observed at day1 and day 3 compared with Group C ($P < 0.05$), with mRNA expression reduced by 25%-60%, before returning to baseline by day 7. In contrast, SYP and PSD-95 mRNA expression patterns diverged markedly between groups: Group S+A showed significant upregulation at days 3 and 7 ($P < 0.05$), whereas Group S+B demonstrated progressive downregulation throughout the intervention period, reaching minimal expression at day 7 ($P < 0.05$). Compared with Group S, both intervention groups maintained comparable levels of BDNF and TrkB mRNA at days 3 and 7 ($P < 0.05$). Notably, SYP and PSD-95 transcripts were significantly upregulated in Group S+A, representing a 53%-93% increase relative to Group S, but downregulated in Group S+B, reflecting a 31%-71% loss in synaptic transcripts. Critically, SYP and PSD-95 mRNA levels were consistently lower in Group S+B than in Group S+A across all time points. These coordinated transcript-level findings, consistent with protein data, indicate distinct recovery kinetics within BDNF/TrkB signaling and persistent dysregulation of synaptic markers dependent on the type of pharmacological intervention (Figure 4D).

Structural analysis via Golgi staining corroborated these findings. Group S+A showed increased dendritic spine density in hippocampal CA1 neurons at days 3 and 7 versus Group S ($P < 0.05$), representing a 31%-34% recovery in synaptic connectivity, whereas Group S+B demonstrated progressive spine loss across all timepoints ($P < 0.05$), corresponding to an additional 43%-74% reduction versus Group S. Intergroup comparisons revealed significantly reduced spine density in Group S+B versus Group S+A throughout the intervention period ($P < 0.05$). These coordinated behavioral, molecular, and structural findings indicate that while both interventions normalized BDNF/TrkB signaling, they produced opposing effects on synaptic plasticity markers and cognitive outcomes (Figure 4B).

Discussion

PND represents a clinically significant psychiatric complication influenced by multiple perioperative factors, including patient age, sex, surgical type, and anesthetic agents [27,28]. Severe PND adversely affects patient recovery and imposes substantial healthcare burdens by limiting medical resource accessibility. Currently, the absence of definitive laboratory diagnostic criteria and effective pharmacological interventions remains a major challenge in PND management. Consequently, elucidating the pathogenic mechanisms of PND, establishing objective biomarker-based diagnostic standards, and developing effective pharmacotherapies for prevention and reversal are critical for improving public health and socioeconomic outcomes. The establishment of a valid PND model requires careful selection among available research systems, including cell cultures, brain slice preparations, and animal models [29,30]. While in vitro models provide valuable mechanistic insights, they inadequately replicate the complex physiological effects of surgical stress and systemic inflammation encountered in clinical settings. Moreover, determining pharmacologically relevant anesthetic dosages and exposure durations necessary to induce translationally meaningful physiological alterations remains challenging.

Although multiple species including nematodes and fruit flies have contributed to understanding basic anesthetic neurotoxicity, rodent models-particularly rats and mice-remain the preferred platform for PND research due to their neuroanatomical and physiological similarities to humans and their capacity to perform sophisticated neurobehavioral tasks. These tasks, such as complex maze navigation, enable robust quantitative assessment of learning and memory functions. Importantly, studies in SD rats have demonstrated that the severity of inhalational anesthetic-induced cognitive impairment exhibits strong correlations with advanced age, sex, and specific pharmacokinetic parameters including drug concentration and exposure duration [31,32]. In this study, PND was modeled through 2-hour inhalation exposure to 3% sevoflurane in 18-month-old male SD rats. Model validation was subsequently performed using Morris water maze testing, which revealed significant cognitive impairment in sevoflurane-exposed groups (S, S+A, S+B) versus carrier gas-treated controls (Group C). Specifically, Groups S, S+A, and S+B exhibited prolonged escape latency ($P < 0.01$), increased swimming distance ($P < 0.01$), reduced platform crossing times ($P < 0.05$), and decreased target quadrant dwell time ($P < 0.05$).

Quantitatively, the impairment in escape latency and swimming distance reached approximately 40%-60% compared to Group C and pre-exposure baselines, while platform crossing frequency decreased by 29%-32%, indicating substantial cognitive deficits. In contrast, Group C showed no statistically significant behavioral alterations following carrier gas exposure. These findings collectively establish a validated PND model replicating clinically relevant anesthetic-induced cognitive deficits in aged rodents, characterized by measurable impairments in spatial learning and memory. The BDNF and its high-affinity TrkB represent a critical signaling pathway modulating hippocampal synaptic plasticity, which is implicated in the pathophysiology of PND. The hippocampus contains particularly high concentrations of BDNF [33], which is packaged into vesicles and released from both dendrites and presynaptic terminals. Upon release, BDNF preferentially binds to TrkB receptors located on the postsynaptic membrane, triggering dimerization and autophosphorylation of the receptor's intracellular tyrosine kinase domain. The phosphorylated TrkB (p-TrkB) subsequently initiates downstream signaling cascades that regulate key neuronal processes including differentiation, survival, and synaptic plasticity [18,34,35].

Dysregulation of BDNF signaling, both within the central nervous system and systemically, has been closely associated with several neurodegenerative conditions [18,35,36]. Evidence has established a

close association between BDNF and Alzheimer's disease (AD), where modulation of BDNF expression can ameliorate AD-related cognitive decline [16,37]. Recent studies further demonstrate that regular physical exercise not only reduces AD risk but also enhances cognitive function and slows disease progression [38]. Notably, emerging research links these neuroprotective effects to exercise-induced BDNF upregulation [39]. Our investigation revealed significant downregulation of BDNF, TrkB, PSD-95, and SYP in the hippocampal CA1 region of PND model rats (Group S) during acute phase (post-intervention day 1 and 3), coupled with reduced dendritic spine density versus Group C ($P < 0.05$). Specifically, protein levels of BDNF and TrkB were reduced by 48%-67%, while SYP and PSD-95 decreased by 10%-20%. At the transcript level, BDNF and TrkB mRNA abundance decreased by approximately 60%, and SYP and PSD-95 mRNA by 30%-40%. Structurally, dendritic spine density in CA1 neurons was reduced by 10%-20%.

These impairments underlie the observed cognitive deficits, with behavioral metrics showing 40%-60% deterioration in learning efficiency. By day 7 post-intervention, spatial learning and memory performance returned to baseline levels, concurrent with normalization of BDNF, TrkB, SYP, and PSD-95 expression and dendritic spine density, indicating spontaneous recovery but highlighting the transient nature of sevoflurane-induced dysfunction. These findings implicate BDNF/TrkB-dependent synaptic plasticity mechanisms in sevoflurane-induced cognitive impairment in aged rats. To interrogate this mechanistic link, Group S+B received intraperitoneal administration of the selective TrkB antagonist ANA-12 (0.25 mg/kg). This intervention exacerbated cognitive decline progressively, with memory retrieval deficits increasing by an additional 15%-55% compared to Group S. Molecularly, SYP and PSD-95 protein levels were further reduced by 15%-52%, and mRNA levels by 31%-71%, while dendritic spine density decreased by an additional 43%-74% versus Group S ($P < 0.05$ at days 3 and 7), demonstrating TrkB signaling's critical role in PND pathophysiology.

Regarding the role of BDNF in improving cognitive function of aging SD rats, in 2010, Jung [40] discovered that 7,8-DHF selectively activates the TrkB receptor. After screening over 2,000 bioactive substances, it was found to mimic the biochemistry of BDNF and possess a small molecular size, facilitating easy penetration across the blood-brain barrier and enabling therapeutic application in multiple diseases [41]. Animal experiments demonstrated that 7,8-DHF enhanced synaptic plasticity by increasing spine density of a Fragile X syndrome mouse model, while also improving recognition of lacunae [21]. To evaluate its therapeutic potential for PND, we administered 7,8-DHF intraperitoneally to sevoflurane-exposed aged SD rats (Group S+A) during modeled procedures. Relative to untreated sevoflurane controls (Group S), 7,8-DHF treatment significantly improved cognitive function, with behavioral metrics showing a 10%-27% recovery in escape latency and swimming distance. Molecularly, SYP and PSD-95 protein expression increased by 8%-40%, and mRNA levels by 53%-93%, while dendritic spine density recovered by 31%-34% compared to Group S. These improvements are mechanistically attributable to 7,8-DHF-mediated TrkB phosphorylation and synaptic plasticity restoration.

Notably, extended administration not only reversed anesthesia-induced deficits but enhanced cognition beyond age-matched controls. Given that age-related cognitive decline increases vulnerability to neurodegeneration [42,43], these findings, with quantifiable recovery degrees, position 7,8-DHF as a candidate therapeutic for mitigating cognitive aging. In conclusion, this study demonstrates that sevoflurane induces transient but substantial cognitive impairments in aged rats, mediated through BDNF/TrkB pathway dysregulation and synaptic plasticity deficits, with measurable damage degrees of 40%-60% in behavior and 10%-67% in molecular markers. Pharmacological modulation via TrkB agonism with 7,8-DHF promotes significant recovery (10%-93% across metrics), whereas antagonism exacerbates damage (15%-74% additional deficits), underscoring the therapeutic potential of targeting this pathway for PND management. Future research should focus on translational studies to validate these findings in clinical settings. Several limitations warrant consideration: First, while BDNF exhibits both central and peripheral distribution with blood-brain barrier permeability [44], this study did not examine sevoflurane or 7,8-DHF effects on peripheral BDNF/TrkB/p-TrkB dynamics.Second, although exercise enhances cognitive reserve and upregulates BDNF expression [39,45,46], our design did not assess whether pre-modeling behavioral training-induced cognitive improvement correlated with BDNF-mediated reserve augmentation.

Third, circadian rhythm disruptions-known modifiers of bioactive factor expression-were not investigated as potential contributors to sevoflurane-induced cognitive alterations. Regarding BDNF biology, the pro-BDNF and mature BDNF (mBDNF) isoforms exert bidirectional synaptic regulation: pro-BDNF binding to p75 neurotrophin receptor (p75NTR) promotes hippocampal long-term depression and apoptosis [20,35,47], contrasting with mBDNF/TrkB-mediated plasticity enhancement. Our focus on central BDNF/TrkB signaling revealed sevoflurane-induced synaptic impairments reversible by BDNF analogs. Ongoing investigations aim to:

1. Determine whether preoperative endogenous BDNF upregulation or exogenous analog administration prevents PND development, and
2. Elucidate synergistic interactions between BDNF/TrkB and complementary cognitive pathways (e.g., CREB, IGF-1) to advance geriatric PND prevention strategies.

Conclusion

Exposure to 3% sevoflurane for 2 hours induced significant cognitive impairment in aged rats, which was mechanistically linked to disrupted BDNF/TrkB signaling and subsequent hippocampal synap-

tic deficits. This cascade involved downregulation of BDNF and TrkB expression, decreased levels of the synaptic proteins PSD-95 and SYP, and reduced dendritic spine density in the CA1 region. Administration of the TrkB agonist 7,8-DHF effectively restored BDNF/TrkB signaling, enhanced synaptic protein expression and spine density, and ultimately rescued cognitive function. These findings demonstrate a causal relationship between sevoflurane-induced impairment of BDNF/TrkB signaling, synaptic structural deficits, and cognitive dysfunction, while highlighting the therapeutic potential of 7,8-DHF in mitigating these effects through targeted modulation of hippocampal plasticity.

Research Ethics

All experimental procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of Inner Mongolia Medical University (Approval No. YKD202101139).

Author Contributions

Conceptualization, XW and CW; methodology, YY; software, YY and HY; validation, WL and NW; formal analysis, JX; investigation, PM; resources, WL; data curation, HY; writing-original draft preparation, YY; writing-review and editing, JX; visualization, PM; supervision, XW; project administration, XW; funding acquisition, XW All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability

All data supporting the findings of this study are available within the paper or its Supplementary Materials, and are also available from the authors upon reasonable request. Newly created materials are available from the authors upon reasonable request. Correspondence and requests for materials, etc., should be addressed to Yurong Yang.

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