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ORIGINAL RESEARCH

Effect of Dexmedetomidine on Apoptosis and Early Cognitive Dysfunction in Rats Following Propofol Anesthesia

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ABSTRACT

Background • To address the intricate interplay between surgical anesthesia, hippocampal apoptosis, and early cognitive dysfunction in rats, this study delves into the impact of dexmedetomidine (DEX). With a focus on understanding the alterations in the PI3K/Akt pathway, our investigation aims to shed light on the comprehensive dynamics of these processes.

Methods • Sixty healthy Sprague-Dawley rats were randomly divided into three groups: controls (intraperitoneal saline injection), group A (intraperitoneal propofol injection), and group A + DEX (intraperitoneal propofol and DEX injection), with 20 rats in each group. Cognitive function in the three groups was evaluated using [specify the cognitive function tests, e.g., Morris Water Maze]. The assessment was conducted at various postoperative time points. We employed Hematoxylin-eosin (HE) staining, flow cytometry (FC), Western blot (WB), and real-time fluorescence quantitation polymerase chain reaction (RT-qPCR) to examine hippocampal apoptosis and gene expression.

Results • Rats in groups A and A + DEX exhibited higher cognitive scores (NSS) and escape latencies at each postoperative time point, along with a lower proportion of swimming distance (SD) in the target quadrant (TQ) compared to controls. Group A + DEX demonstrated lower NSS and escape latency than controls, accompanied by a higher proportion of SD in TQ. Apoptosis rates of hippocampal cells were higher in groups A and A + DEX than in controls, although they were relatively lower in group A + DEX ($P < .05$). Regarding gene expression, the relative expression (RE) of *Bcl-2, PI3K, pAkt,* mRNA expression of *Bcl-2* and *PI3K*, and *Bax* and *caspase3* were altered. Group A + DEX showed higher RE of *Bcl-2, PI3K, pAkt,* mRNA expression of Bcl-2 and *PI3K*, and lower *Bax* and *caspase3* than group A ($P < .05$). For a detailed understanding of the magnitude of these changes, specific values or ranges are provided in the subsequent results section.

Conclusion • In conclusion, the combined use of surgical anesthesia with DEX demonstrates a modulatory effect on the *PI3K/Akt* signaling pathway. This intervention proves effective in reducing hippocampal cell apoptosis post-surgery, thereby alleviating neurological impairments and ameliorating early cognitive dysfunction in rats. Our findings underscore the potential therapeutic impact of DEX in enhancing cognitive outcomes following surgical procedures.

The observed reduction in hippocampal cell apoptosis and improvement in cognitive function suggest that DEX may hold promise as a neuroprotective agent in the perioperative setting. These outcomes highlight the clinical relevance of considering DEX as an adjunctive therapy to mitigate cognitive dysfunction associated with surgery. Further investigations and clinical trials are warranted to validate and extend these findings, potentially offering a novel avenue for improving patient outcomes and advancing perioperative care strategies. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

With the rapid development of global medical technology, the number of patients treated with surgery is increasing. In China, the increasingly aging population has drawn attention to cognitive dysfunction following surgical anesthesia. Commonly used anesthesia drugs include sufentanil and propofol, both known for their rapid onset and recovery in general anesthesia administration for surgeries.[1,2] However, clinical studies have found that sufentanil and propofol can induce neurotoxicity during use,

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induce neuronal apoptosis, reduce the density of dendritic spines, and even cause cognitive dysfunction.[3,4] This concern highlights the need for a closer examination of the impact of these drugs on cognitive function.

Postoperative cognitive dysfunction (POCD) is an acute, fluctuating mental disorder syndrome that can be reversed clinically.[5] Previous studies have indicated that the incidence of POCD ranges from 20% to 40% in individuals aged 60 years or older.[35] Surgical stress and inflammation are contributing factors to the occurrence of POCD.[36] The main clinical manifestations of POCD are a decrease in memory, learning, behavior, cognitive ability, and orientation and positioning ability, which lasts for weeks, months, years, or even longer.[6] Hippocampus is the main site of advanced neural activities such as memory and learning. Hippocampal long-term potentiation (LTP) is the cellular basis of memory and learning. Studies have suggested that there is a certain relationship between neurological impairment and hippocampal cell apoptosis.[7] However, the relationship between POCD and the normality of the hippocampus needs further study. In addition, relevant statistics show about 6% of adult patients with POCD, while about 13% of elderly patients around 3 months after surgery.[8] Given the unclear specific mechanism of POCD in clinical practice, effective prevention and treatment remain challenging.

Dexmedetomidine (DEX) belongs to a new type of α2 adrenoceptor agonist, which has a very high affinity with α2 adrenoceptor and is a highly selective receptor agonist commonly applied in clinical practice.[9] DEX can stimulate α2 adrenal receptors to play the functions of sedation, analgesia, anti-sympathetic nerve activity, and hemodynamic stability, and there is no respiratory or inhibitive reaction.[10] Some studies have found that DEX can reverse nerve apoptosis and brain function damage caused by anesthetics in rats.[11] DEX can protect against ischemia-reperfusion brain injury by alleviating stress response and inflammatory response, activating related signaling pathways, and reducing apoptosis of nerve cells.[12,13]

Phosphatidylinositol 3-kinase (*PI3K*), composed of regulatory subunit p85 and catalytic subunit p110 encoded by the *PIK3CA* gene, and protein kinase B (*Akt*), a cytoplasmic serine-threonine protein kinase, promote cell cycle progression and inhibit apoptosis when activated through phosphorylation at T308 and S473 [*pAkt*].[37] Wang et al. (2022)[14] confirmed that DEX can activate *PI3K/Akt* pathway to inhibit apoptosis and inflammation induced by hypoxia/ reoxygenation (H/R) in MIRI. The *PI3K/Akt* pathway exists in various nerve cells and is one of the important ways for receptor cell signals on the cell membrane to be transmitted to the cells.[15] At present, studies have confirmed that DEX improves the cognitive ability of patients undergoing gastric cancer surgery and alleviates the expression of postoperative inflammatory factors by regulating the *PI3K/Akt* pathway.[16]

In summary, this study employed rats as experimental subjects to delve into the influence of DEX on POCD and apoptosis in the rat hippocampus following anesthetic administration. Our investigation also scrutinized the impact of DEX on the PI3K/Akt pathway. By tackling these specific objectives, our research seeks to bridge existing knowledge gaps and offer insights that could potentially contribute to enhancing the clinical management of patients undergoing surgical anesthesia. This study addresses the need for a deeper understanding of the mechanisms underlying POCD and the potential neuroprotective role of DEX in the perioperative context. As we unfold our findings, we aim to shed light on novel avenues for interventions and advancements in perioperative care.

MATERIAL AND METHOD

Material and instrument

Sprague-Dawley rats (Experimental Animal Center of Fujian Medical University), DEX (Hunan Huateng Pharmaceutical Co., Ltd., Specification: 2 mL; 200 g), propofol (Shanghai Yuewei Chemical Co., Ltd., 10 mg/ml, 200 mg/20 ml), reverse transcription kit (Med Chem Express), rabbit anti-rat PI3K monoclonal antibody, Akt monoclonal antibody, phosphorylated Akt (pAkt) polyclonal antibody, serum B-cell lymphoma-2 (Bcl-2), Bcl-2 associated X protein (Bax), cysteine protease (Caspase)-3 (primary antibody), goat anti-rabbit PI3K, Akt, p-Akt, Bcl-2, Bax, Caspase-3 (secondary antibody) (Abeam USA), fetal bovine serum, trypsin, penicillin, streptomycin double antibody (Gibdo, USA), RIPA lysis solution (Thermofisher (China) Co., Ltd.), hematoxylin, eosin (Zhongshan Aobo Biotechnology), trypsin, phosphate buffer solution (PBS), TBST solution (Cangzhou Sunsonzyme Biotechnology Co., Ltd.), flowcytometry (FC) (Beckman Coulter International Trade (Shanghai) Co., Ltd.).

In this study, we utilized advanced instruments including the CM-120 transmission electron microscope (Nikon, Japan) to examine cellular structures, the RT-qPCR instrument (Bio-rad, USA) for precise genetic analysis, and the Morris water maze (MWM) (XR-XM101; Beijing Shuolinyuan Technology Co., Ltd.) for behavioral assessments. MWM, a round stainless steel pool with a diameter of 120 cm and a height of 50 cm, with four water points on the pool wall, divides the pool into four elephant boundaries. The CM-120 transmission electron microscope provided high-resolution imaging for detailed cellular analysis, enhancing our ability to investigate structural changes. These instruments collectively enabled a comprehensive exploration of cellular and molecular aspects alongside behavioral outcomes.

Experimental animal

The 60 research animals used in this study were healthy Sprague-Dawley rats, aged between 2-6 weeks, with an average age of (4.23±1.09) weeks. The weight of these rats ranged from 192-219 g, with an average weight of (204.33±7.72) g. All rats were housed in an environment with a relative humidity of 40% ~ 45% and a temperature of (23.8±1.5)°C for 1 week, with a 12-hour light exposure each day.

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The rats were randomly divided into four groups: the control group, the propofol group (Group A), and the propofol + DEX group (Group A + DEX), with 20 rats in each group. The control group received an intraperitoneal injection of 50 μg/kg of normal saline. The rats in the control group had a mean age of (4.12±1.03) and a mean weight of (209.29±7.09) g. Group A received 100 mg/kg of propofol. The rats in Group A had a mean age of (4.45±1.32) and a mean weight of (201.82±7.01) g. Group A + DEX was administered 50 μg/kg of DEX in addition to 100 mg/kg of propofol. The rats in Group A + DEX had a mean age of (4.01±1.22) and a mean weight of (210.09±7.56) g. It's important to note that there were no significant differences in age and weight among the three groups ($P > .05$), indicating the feasibility of the experimental design.

The Sprague-Dawley rats used in this study were sourced from the Experimental Animal Center of Fujian Medical University. The research involving animals was conducted in compliance with ethical guidelines and was approved by the relevant animal ethics committee of The First Hospital of Nanping City. There were no conflicts of interest associated with this research, and any external sources did not fund it.

Improved NSS

At 1, 4, and 7 days following the operation, the NSS scale was adopted to evaluate the degree of neurological deficit. The experiments in the improved NSS can be divided into motion, sensory, balance, and reflection tests. The motion test includes tail lifting and walking tests. The total score of tail lifting and walking tests is 3; sensory, balance, and reflection tests are 2, 6, and 4; and the total score is 18. The higher the NSS, the more serious the neurological deficit. The specific experimental methods are given in Table 1.

MWM test

Cognitive function in rats was assessed using the MWM test.[17] The MWM consisted of a circular swimming pool with a diameter of [specify the diameter] and was maintained at a constant water temperature of approximately 25°C. The pool was divided into four quadrants. The hidden platform, measuring [specify dimensions] and positioned 1 cm below the water's surface, was placed in the first quadrant. An overhead camera was installed to capture and record the movement trajectories of the rats. The water entry point and experimental time were set, and the rats were allowed to become familiar with the environment in the water maze for 3 days before the experiment. The positioning cruise test was performed on the 8th to 11th day after the operation. A quadrant of the water entry point was randomly selected to gently place the rats into the pool facing the wall, and timing was started. The time of rats entering the platform within 1 min was recorded, which was the escape latency. Those who were not found within 1 min were guided by the experimenter. The escape latency of these rats was recorded as 1 min; each quadrant 1/d, 4 times/d, every 2h into the water once. The space exploration test was performed 12 d after the operation, the platform was removed, the water entry point was randomly selected, the 1 min swimming track of rats was recorded, and the proportion of swimming distance (SD) in the target quadrant (TQ) was calculated. The calculation method is shown in Equation (1).

Table 1. NSS scale

Test type	Specific operation	Score
Tail lifting test	Buckling forelimb	1
	Buckling hind limbs	1
	The head deviates from the vertical line by more than 100° within 30 s	1
Walking test	Normal	0
	Not able to walk in a straight line	1
	Turn to the affected side	2
	Toppling to the affected side	3
Sensory test	Visual and tactile testing	1
	Stimulating muscle to detect deep sensation	1
Balance test	Standing stably on the balance beam	0
	Grasping the edge of the balance beam	1
	Grasping the balance beam, one limb down	2
	Grasping the balance beam, one limb down or rotate more than 60 s.	3
	Dropping on the balance beam for more than 40 s	4
	Dropping on the balance beam for more than 20 s	5
	Dropping	6
Reflection experiment	Shaking head when touched the external auditory canal	1
	Blinking while touched the cornea	1
	Motion response due to noise	1
	Loss of motor function	1

(1)

$$D_p = \frac{D_I}{D_{all}} \times 100\%$$

The calculation method is shown in Equation (1), where SD represents the swimming distance, and TQ represents the target quadrant. D_p means the proportion of SD in TQ. D_I indicates the SD in quadrant I. D_{all} represents the total SD.

HE staining

After the cognitive dysfunction and neurological impairment of all rats were tested, the rats were sacrificed by cervical dislocation, and the hippocampus of the rats was extracted. Then, it was placed in 15% methanol for fixation and then inserted in conventional paraffin for serial sections. The thickness of the section was about 3 μm, and finally, HE staining was carried out.

FC detection

FC detected the apoptosis rate of hippocampus in three groups. The hippocampal tissue cells were transfected with plasmids for 24 hours and then digested with 0.25 ml trypsin for 5 minutes until the mist-like substance appeared in the cell bottle. Then, PBS was adopted to blow the mist-like substance into the bottle. At 4°C, centrifugation was carried out at 2000 r for 3 min. After that, it was washed with PBS, centrifuged, and resuspended twice. Finally, the apoptosis was analyzed by FC.

WB

Part of the hippocampus of the rats was taken and ground with liquid nitrogen. Following washing with PBS, RIPA lysate was put to lyse the cells for half an hour. Following a boiling water bath for 9 min, it was centrifuged at 12 000 r for 15 min, and the supernatant was taken for protein concentration detection. The 30 μm sample was mixed in protein buffer, and electrophoresis was carried out

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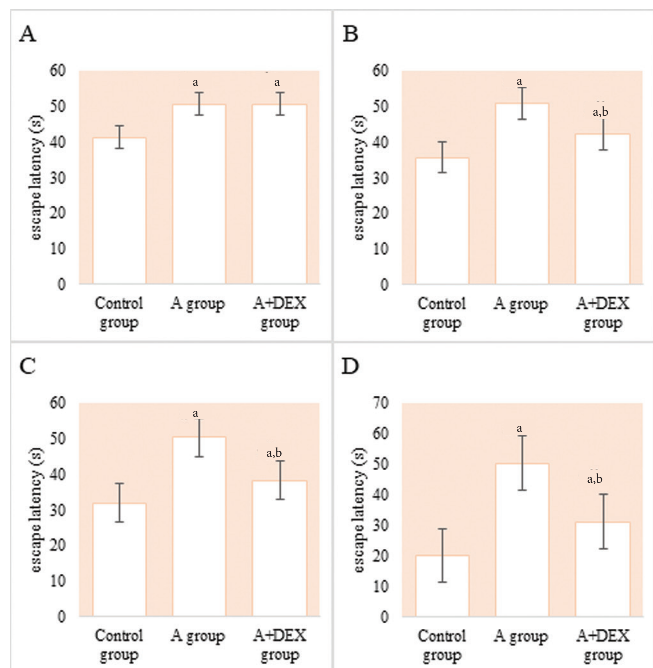
Table 2. Primer sequences

Gene	Upstream primer	Downstream primer
Bcl-2	5’-GGACAACATCGCCCTGTG-3	5’-AGTCTTCAGACAGACAGCCAGGA-3’
Bax	5’-GCCGAAATGTTTGCTGACG-3’	5’-CCGATCTCGAAGGAAGTCCA-3’
caspase3	5’-AAGGCAGAGCCATGGACCAC-3’	5’-CTGCCTCTTCCCCCATTATGCC-3’
PI3K	5’-TATTTGGACTTTGCGACAAGACT-3’	5’-TCGAACGTACTGGTCTGGATAG-3’
Akt	5’-AGCATGGAGTGTGTGGACAG-3’	5’-TACAGATGATCCATGCGGGG-3’

Figure 1. Comparison of Neurological Severity Scores (NSS) among Three Groups after Operation**.** Group A+DEX showed lower NSS than group A at 4 and 7 days, indicating a potential neuroprotective effect (A: day 1, B: day 4, C: day 7)



[a]relative to controls, $P < .05$
[b]relative to group A, $P < .05$

for 10 min. The electron transfer membrane was immersed in 10% milk and sealed at ambient temperature for 90 min. Following washing with PBS, the diluted primary antibody was put and incubated overnight at 4°C. After it was taken out, the TBST solution was adopted to rinse, and then the diluted secondary antibody was put. After incubation for an hour at room temperature, the cleaning and coloration were carried out. The gel imaging system was applied to scan the target protein. The ratio of the gray value of the target protein to the internal reference β-actin represented the RE of the protein to detect the expression of Bcl-2, Bax, caspase3, PI3K, Akt, and pAkt.

RT-qPCR

RT-qPCR was applied to test the mRNA expression of Bcl-2, Bax, caspase3, PI3K, and Akt in the hippocampus of rats. Part of the hippocampus was taken. The hippocampus was cut, extracting the total RNA content. The RNA was reversed into complementary DNA (cDNA) by reverse transcription kit. After identification, RT-qPCR analysis was performed. Reaction conditions: pre-denaturation at 90°C for 4 min; then denaturation at 90°C for 30 s, annealing at 60°C for 30 s, extension at 70°C for 40 s, it was repeated 30 times. With β-actin as the reference, the RE of different genes was computed by $2^{-\Delta\Delta CT}$, it was repeated three times, and the average value of CT was obtained. The specific primer sequence is given in Table 2**.**

Statistical methods

SPSS 25.0 software was applied for statistical analysis. Measurement data were presented as mean standard deviation (±s). Repeated measures analysis of variance was adopted for contrast of repeated measurement data, LSD-t test for pairwise contrast. Single-factor analysis of variance was adopted to compare the measurement data of multiple samples, and the SNK-q test was used for pairwise comparison. $P < .05$ meant the difference had statistical meaning.

RESULTS

Comparison of NSS

Figure 1 depicts the comparison of NSS among rats in the control group, group A, and group A+DEX at 1, 4, and 7 days following the operation. The NSS on days 1, 4, and 7 after the operation were (2.12±0.39), (1.96±0.41), and (1.85±0.35) in the control group, respectively. In group A, the NSS were (8.32±1.01), (8.97±0.82), and (7.78±0.68) for the corresponding days. Group A+DEX had NSS of (7.27±1.04), (4.09±0.57), and (3.16±0.78) for the same time points. Statistical analysis revealed that compared to the control group, the NSS of rats in groups A and A+DEX at 1, 4, and 7 days after the operation were higher. Relative to group A, the NSS in group A+DEX was lower at 4 and 7 days following the operation ($P < .05$). There was no significant difference on the 1st day after the operation ($P > .05$).

Comparison of MWM test results

Comparison of escape latency. Figure 2 illustrates the escape latency comparison of rats on the 8th, 9th, 10th, and 11th day post-operation. The escape latency of controls was (41.34±4.32) seconds, (35.78±3.44) seconds, (31.98±3.68) seconds, and (20.21±2.69) seconds on the 8th, 9th, 10th, and 11th day following the operation. The escape latency in group A was (50.66±5.76) seconds, (50.88±5.03) seconds, (50.43±5.17) seconds, (50.37±5.15) seconds; The escape latency in group A + DEX was (50.63±5.29) seconds, (42.31±4.32) seconds, (38.39±3.54) seconds, (31.24±3.53) seconds. The escape latency in the groups A and A + DEX was longer on the 8th, 9th, 10th, and 11th days post-operation; in contrast with group A, the escape latency in group A + DEX was decreased on the 9th, 10th, and 11th day post-operation ($P < .05$).

Proportion of SD in TQ. Figure 3 illustrates the proportion of SD in TQ of rats 12 days after operation. The proportion of SD in TQ was (50.03±5.88)% in controls, (25.21±3.01)% in group A, and (37.44±3.75)% in group A + DEX. The proportion of SD in TQ in groups A and A + DEX was lower at 12 days post-operation; relative to group A, the

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Figure 2. Contrast of escape latency of three groups of rats. Group A+DEX demonstrated a reduction in escape latency compared to group A on the 9th, 10th, and 11th days post-operation (A, B, C, D: the 8th, 9th, 10th, and 11th day post-operation)

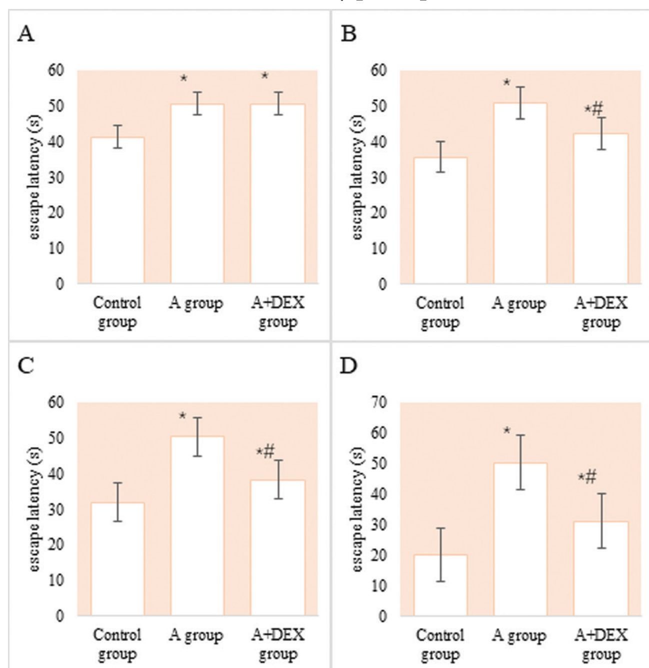


Figure 3. Contrast of swimming distance (SD) in the target quadrant (TQ) in rats. Groups A and A+DEX exhibited lower proportions than controls; however, group A+DEX showed an increase compared to group A

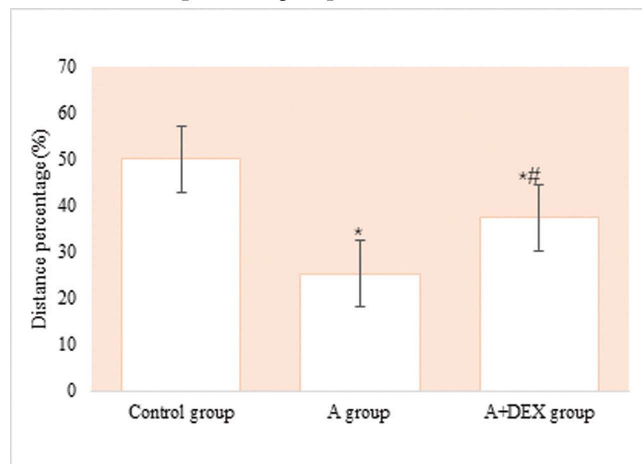


Figure 4. Hematoxylin-eosin (HE) staining results of the hippocampus. In rats, HE staining revealed that in the control group, the hippocampal structure was intact with a well-defined nucleolus and clear organelle structure. (A indicates controls, B indicates group A, C indicates group A + DEX)

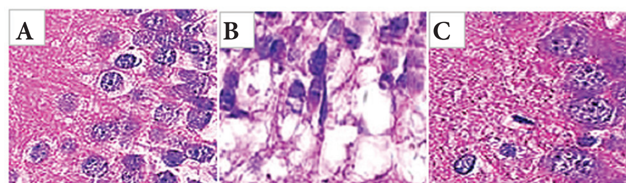
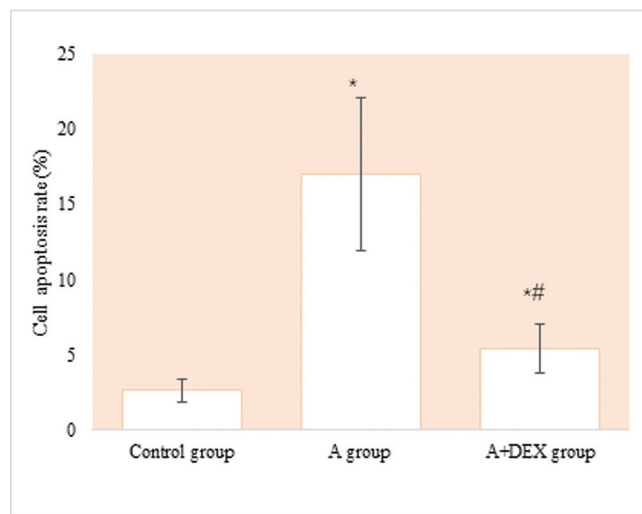


Figure 5. Contrast of apoptosis rate in rat hippocampus.



proportion of SD in TQ in group A + DEX increased at 12 days post-operation ($P < .05$).

HE staining results of the hippocampus in rats

HE staining was performed on the hippocampus in rats to observe the structure of the hippocampus. In controls, the morphological structure of the hippocampus of the rats was basically complete, the nucleolus was basically present, and the structure of the organelles was clearly displayed. In group A, the nucleus of the hippocampus of the rats was obviously swollen, the density of chromatin was obviously reduced, and the cell structure was damaged. Relative to group A, in group A + DEX, the damage of hippocampal tissue and cell structure was clearly reduced, the nuclear swelling was relieved, and the density of mitochondria and chromatin was basically normal (Figure 4).

Comparison of apoptosis rate in rat hippocampus

Figure 5 compares the apoptosis rate in the hippocampus of rats within 48 hours. The apoptosis rate of the hippocampus was (2.62±0.23)% in controls, was (17.02±2.43)% in group A, and was (5.39±0.73)% in group A + DEX. The apoptosis rate of the hippocampus in groups A and A + DEX raised; as against group A, the apoptosis rate of the hippocampus in group A + DEX was decreased ($P < .05$).

RE of *Bcl-2, Bax, caspase3, PI3K, Akt,* and *pAkt* in hippocampus

In controls, the RE of *Bcl-2, Bax, caspase3, PI3K, Akt, pAkt* was (1.61±0.29), (0.99±0.05), (0.78±0.02), (1.42±0.01), (0.97±0.04), (0.23±0.03); the RE of those in group A was (0.66±0.07), (1.93±0.12), (1.45±0.07), (0.21±0.09), (0.95±0.02), (0.78±0.01); the RE of those in group A + DEX was (1.22±0.18), (1.17±0.17), (0.94±0.03), (0.89±0.02), (1.01±0.01), (0.53±0.01). Therefore, in groups A and A + DEX, the RE of *Bcl-2*, *PI3K*, and *pAkt* in rats decreased, and *Bax* and *caspase3* increased ($P < .05$), without obvious

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Figure 6. Contrast of Relative Expression (RE). (A) Serum B-cell lymphoma-2 (*Bcl-2*); (**B**) *Bcl-2* associated X protein (*Bax*); (**C**) Cysteine protease *Caspase-3*; (**D**) Phosphatidylinositol 3-kinase (*PI3K*); (**E**) Protein kinase B (*Akt*); (**F**) *pAkt*

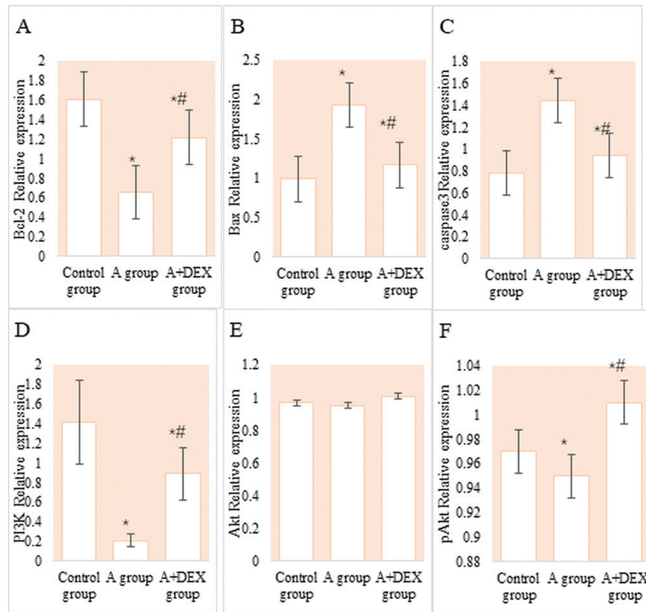
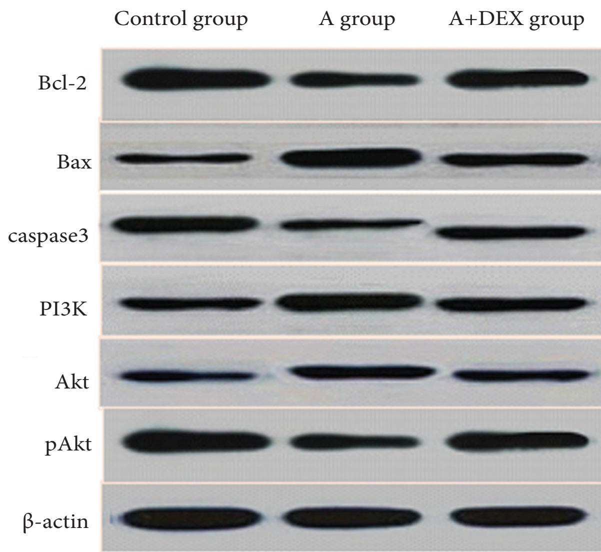


Figure 7. Western blot.



distinction in the RE of *Akt* ($P > 0.05$). As against group A, the RE of *Bcl*-2, *PI3K*, and *pAkt* in group A + DEX raised, and Bax and caspase3 decreased ($P < .05$). The RE of *Akt* had no obvious distinction ($P > .05$) (Figure 6). Figure 7 illustrates the results of WB.

mRNA expression of *Bcl*-2, *Bax*, *caspase3*, *PI3K*, and *Akt* in rat hippocampus

RT-qPCR suggested the mRNA expression level of *Bcl-2* and *PI3K* was decreased, and that of *Bax* and *caspase3* was increased in groups A and A+DEX ($P < .05$), without obvious distinction in *Akt* ($P > .05$). as against group A, the level of *Bcl-2* and *PI3K* was enhanced, and *Bax* and *caspase3* were decreased ($P < .05$), without obvious distinction in *Akt* ($P > .05$) (Table 3).

Table 3. mRNA expression (RT-qPCR Results)

mRNA Index	Controls (n = 20)	Group A (n = 20)	Group A+DEX (n = 20)
Bcl-2	0.92±0.05	0.32±0.03	0.68±0.06
Bax	0.86±0.07	1.89±0.18	1.21±0.11
caspase3	0.43±0.03	1.07±0.02	0.79±0.04
PI3K	0.94±0.08	0.38±0.03	0.63±0.05
Akt	0.92±0.05	0.91±0.02	0.89±0.04
RT-qPCR result			
Bcl-2			
Bax			
caspase3			
PI3K			
Akt			
β-actin			

DISCUSSION

The primary objective of our study was to investigate the impact of anesthesia, a crucial intervention in clinical surgical procedures, on long-term functional abnormalities, particularly those related to central nerve injury. Anesthesia, while essential for inhibiting pain sensation during surgery, has been associated with lasting functional changes.[18,19] It was found the occurrence of the above phenomena is closely related to the central nerve injury caused by anesthesia.[20,21] As against controls, the NSS of rats in group A were superior on the 1st, 4th, and 7th days following the operation, and the escape latency was longer on the 8th, 9th, 10th, and 11th days following the operation. The proportion of SD in TQ was inferior on the 12th day after surgery ($P < .05$). A water maze test was carried out to evaluate the ability of rats to collect, integrate, and learn complex information.[22] The completion of finding the TQ was closely related to the damage of hippocampal structure and function and central nervous system function.[23] The learning and memory abilities of rats anesthetized with propofol were clearly lower than those of non-anesthetized rats. However, other studies have pointed out that there is a certain relationship between neural function damage and apoptosis of hippocampal cells in rats.[24,25] FC showed that as against controls (2.62±0.23)%, the apoptosis rate of hippocampal cells in group A (17.02±2.43)% was increased ($P < .05$). It can be concluded that apoptosis in the hippocampus of rats is related to the level of learning and memory function in rats. Moreover, apoptosis in the hippocampus is correlated with the expression of varieties of proteins and the regulation of signaling pathways.[26] By detecting the RE of *PI3K, Akt, pAkt*, and the mRNA expression of *PI3K* and *Akt*, the RE of *Bcl-2, PI3K, pAkt*, and the mRNA expression of Bcl-2 and PI3K decreased, and the expression

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of Bax and caspase3 increased in group A ($P < .05$). Therefore, propofol can regulate the apoptosis of hippocampal cells through PI3K/Akt pathway by regulating *Bcl-2, Bax, caspase3*, and other apoptosis-related factors. Stekic et al.[27] proposed that the *PI3K/Akt* pathway influences the regulation of apoptosis, cell growth, learning, and memory, which affects the cognitive function of rats.

It has been found that DEX not only exerts analgesic and anti-sympathetic functions by stimulating α2-AR in the brain and spinal cord but also has neuroprotective effects on brain injury caused by various reasons.[28,29] As against the rats in group A, the rats in group A+DEX clearly had lower NSS on the 4th and 7th day following operation and evidently lower escape latency on the 9th, 10th, and 11th day following operation. The proportion of SD in TQ increased 12 days post-operation ($P < .05$). Given the critical role of the *PI3K/Akt* pathway in neurological and cognitive functions, the findings in our study, which demonstrate that DEX can activate this pathway, highlight the therapeutic potential of DEX in a range of neurological conditions. Burlacu et al.[30] proposed that DEX could be applied to prevent cerebral ischemia, traumatic brain injury (TBI), spinal cord injury, neurodegenerative diseases, and postoperative cognitive impairment. These applications could be partly attributed to the pathway's ability to promote neuroprotection and improve cognitive function. Sha et al.[31] also concluded that DEX improves the proliferation and differentiation of developing neural stem cells (NSC) damaged by ketamine, thereby improving cognitive dysfunction. In conclusion, the *PI3K/Akt* pathway's broader relevance in neurological and cognitive functions underscores the potential therapeutic applications of compounds like DEX in various neurological conditions and cognitive disorders. Further research in this area is warranted to explore the full extent of these therapeutic possibilities.

Xing et al.[32] demonstrated that DEX has the potential to inhibit propofol-induced hippocampal neuronal injury in rats through mechanisms involving the up-regulation of SIRT1 and activation of the PI3K/Akt pathway. The study found a significant reduction in the apoptosis rate of hippocampal cells in the group treated with both propofol and DEX (group A+DEX, 5.39±0.73%) compared to the group treated with propofol alone (group A, 17.02±2.43%). Additionally, the expression (RE) of anti-apoptotic marker Bcl-2, as well as PI3K and phosphorylated Akt (pAkt), was elevated in the group A+DEX, while pro-apoptotic markers Bax and caspase3 were decreased ($P < .05$). The observed up-regulation of SIRT1 by DEX is particularly noteworthy. SIRT1 is a protein associated with cellular stress responses and longevity. Its primary function involves deacetylating various target proteins, including transcription factors, and such deacetylation has far-reaching implications on gene expression patterns. In the context of our study, DEX may modulate SIRT1 to regulate specific genes involved in the *PI3K/Akt* pathway and apoptosis.

The *PI3K/Akt* pathway is a well-known signaling cascade with pivotal roles in cell survival, growth, and proliferation. Activation of this pathway has been associated with neuroprotection and cognitive function. *Akt*, a downstream effector of *PI3K*, exerts anti-apoptotic effects by phosphorylating and inactivating pro-apoptotic proteins. The up-regulation of *PI3K* and *pAkt* observed in the presence of DEX suggests a potential mechanism through which DEX may protect hippocampal neurons from apoptosis induced by propofol. Therefore, our study suggests that DEX's neuroprotective effects may be attributed, at least in part, to its modulation of the SIRT1 protein and activation of the *PI3K/Akt* pathway. These molecular mechanisms, involving the delicate balance of pro- and anti-apoptotic factors, provide insights into the potential pathways through which DEX mitigates propofol-induced hippocampal neuronal injury. Further elucidation of these mechanisms could contribute to the development of targeted interventions for preventing or treating cognitive dysfunction in the perioperative setting.

When DEX activates *PI3K* (phosphatidylinositol-3-kinase), it triggers a cascade of events. *PI3K* phosphorylates *Akt* (also known as protein kinase B), causing a conformational change that allows *Akt* to translocate to the cell membrane. Once at the membrane, *Akt* becomes pAkt, the active form of the protein. *pAkt* is a critical regulator of cell proliferation and survival, and it exerts anti-apoptotic effects by phosphorylating a range of downstream targets.[33,34] The observed increase in pAkt levels is significant, as pAkt is known to regulate various cellular processes, including the inhibition of apoptosis. Activated *Akt* can phosphorylate and inhibit pro-apoptotic proteins like Bax, reducing their activity. At the same time, pAkt can promote the expression of anti-apoptotic proteins like Bcl-2. This balance between pro- and anti-apoptotic factors mediated by pAkt likely contributes to the decreased apoptosis rate observed in group A+DEX.

Above all, our findings carry significant clinical implications for the prevention and treatment of POCD, a common complication in surgical patients, particularly in the elderly. POCD is associated with prolonged hospital stays, increased healthcare costs, and diminished quality of life. Recognizing the neuroprotective potential of DEX in the context of anesthesia opens avenues for clinical interventions aimed at mitigating cognitive decline in surgical patients. DEX, with its capacity to activate the *PI3K/Akt* pathway and reduce apoptosis, emerges as a promising candidate for preventing or ameliorating POCD.

In conclusion, our study not only highlights the promising role of DEX in preventing or ameliorating POCD but also underscores the transformative potential it holds for enhancing patient care outcomes. These findings pave the way for future research and clinical endeavors aimed at refining and implementing strategies that can positively impact the cognitive well-being of surgical patients, thereby addressing a critical aspect of postoperative care.

Additionally, the findings emphasize the broader relevance of the *PI3K/Akt* pathway in neurological and cognitive functions. This pathway is involved in various

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aspects of brain function and may have therapeutic applications beyond anesthesia-related cognitive dysfunction. Studies have suggested that DEX has neuroprotective effects in the context of brain injury, neurodegenerative diseases, and other neurological conditions. These applications are likely linked to the pathway's ability to promote neuroprotection and improve cognitive function.

By comparing our findings with existing studies, we contribute to the growing body of knowledge in the field. While our results align with some previous research, discrepancies may arise due to variations in study designs, patient populations, or experimental conditions. Understanding these nuances is crucial for advancing our comprehension of DEX's therapeutic potential and the intricacies of the *PI3K/Akt* pathway in diverse neurological contexts. Future research endeavors should delve into these complexities to unlock novel therapeutic approaches for cognitive dysfunction.

Despite the valuable insights gained from our study, several limitations need to be carefully considered. Firstly, the use of a rat model, while common in preclinical research, introduces inherent differences between rodents and humans. These distinctions may impact the translatability of our findings to clinical scenarios, emphasizing the need for cautious interpretation. Additionally, the focus on propofol anesthesia in this study raises the necessity to acknowledge that various anesthetic agents are employed in clinical practice, each potentially influencing cognitive outcomes differently. Our results may not be universally applicable to other anesthetics.

Moreover, while our study proposes that DEX exerts neuroprotective effects through the up-regulation of SIRT1 and activation of the PI3K/Akt pathway, the underlying mechanisms are intricate and likely involve numerous intermediaries. Further research is imperative to unravel the complexities of these interactions and provide a more comprehensive understanding. In the pursuit of clinical relevance, it is crucial to recognize that the extrapolation of animal study outcomes to human applications demands careful consideration of species-specific variations and potential confounding factors.

In conclusion, our study suggests that DEX may offer protective effects against hippocampal neuronal injury induced by anesthesia, particularly propofol, through the up-regulation of SIRT1 and activation of the PI3K/Akt pathway. Understanding these underlying mechanisms not only sheds light on the neuroprotective properties of DEX but also opens avenues for the development of targeted interventions aimed at reducing POCD. This is particularly relevant for surgical patients, especially those at a higher risk for cognitive impairment.

Looking ahead, further research is essential to explore the full extent of DEX's therapeutic potential and unravel the intricacies of its interactions with signaling pathways. Specific areas warranting attention include: First, investigating the dose-dependent effects of DEX to determine the optimal therapeutic range for neuroprotection. Assessing the enduring impact of DEX on cognitive function to ascertain its potential for sustained neuroprotection beyond the immediate postoperative period. Moreover, conducting comparative studies with various anesthetic agents to delineate the differential impact on cognitive function and identify agents with favorable profiles. Finally, delving deeper into the intricate molecular mechanisms involved in the interaction between DEX, SIRT1, and the *PI3K/Akt* pathway to uncover novel targets for intervention. Furthermore, evaluation and feedback in relevant knowledge in clinical medicine is extremely important [38]. By addressing these research directions, future studies can build upon our findings, contributing to a more comprehensive understanding of DEX's therapeutic potential and advancing innovative approaches in the prevention and treatment of cognitive dysfunction in the postoperative period.

CONCLUSION

In summary, our findings underscore the effectiveness of DEX in modulating the PI3K/Akt signaling pathway, resulting in the inhibition of hippocampal cell apoptosis, mitigation of neurological damage, and improvement in early cognitive dysfunction following surgery in rats. These outcomes hold promise for potential clinical applications, offering insights into novel therapeutic avenues. However, it is essential to emphasize that while this study establishes a robust foundation, the transition to clinical applicability and translation necessitates further exploration and confirmation in human subjects.

The demonstrated neuroprotective effects of DEX present a compelling rationale for future investigations that extend beyond the preclinical stage. Confirmatory studies involving human subjects are imperative to validate the translational potential of DEX in the perioperative context. If proven effective, DEX could emerge as a valuable adjunctive therapy in surgical settings, particularly for patients at risk of postoperative cognitive dysfunction.

In conclusion, our study contributes valuable insights into the intricate interplay between DEX, the PI3K/Akt pathway, and cognitive outcomes. As we move forward, bridging the gap between preclinical evidence and clinical practice remains a crucial step, with the ultimate goal of improving patient outcomes and refining perioperative care strategies.

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