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Experimental study on the effects of dexmedetomidine via the mTOR signaling pathway on cognitive function in POCD rats after partial hepatectomy

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Abstract: **Background**: Postoperative cognitive dysfunction (POCD) frequently occurs after liver resection and is potentially mediated by the mTOR signaling pathway. Although dexmedetomidine, an α2 receptor agonist, exhibits neuroprotective effects, it remains unknown whether it improves post-resection cognitive function by modulating the mTOR pathway. **Objectives**: To discuss the influence of dexmedetomidine on the mTOR signaling pathway in the hippocampus of POCD rats after partial hepatectomy. **Methods**: Thirty Wistar rats were randomly divided into three equal groups: normal, model and treatment. The treatment group received dexmedetomidine, whereas the other two groups received saline. Histopathology, cognitive function and related gene/protein expression were compared among groups received saline. **Results**: The treatment group showed improved hippocampal neuronal structure and arrangement compared to the model group, though still below normal levels; neural apoptosis was significantly reduced ($P<0.05$), and spatial learning and memory were enhanced; Akt expression was partially restored, while mTOR, NF-κB and TNF-α expression (protein/mRNA) remained higher than normal but significantly lower than in the model group ($P<0.05$). **Conclusion**: Dexmedetomidine ameliorates postoperative cognitive dysfunction in rats after liver resection by inhibiting the hippocampal mTOR pathway, reducing neuronal damage and inflammation.

Keywords: Cognitive; Dexmedetomidine; Hippocampus; Hepatectomy; Target of rapamycin protein

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a common complication following liver resection and primarily affects the central nervous system. It is characterized by memory impairment and reduced learning ability. These symptoms typically last for seven days or longer and adversely affect postoperative recovery (Suraarunsumrit *et al*., 2024). Therefore, early intervention is the key to preventing and treating cognitive dysfunction after partial hepatectomy.

Currently, the exact pathophysiological underlying POCD remain incompletely understood. It is believed to involve various pathological processes, including neuroinflammatory activation, oxidative stress, synaptic dysfunction and neuronal apoptosis (He *et al*., 2024). Although some drugs (such as nonsteroidal anti-inflammatory drugs and cholinesterase inhibitors) have shown potential in animal experiments, effective, highly specific prevention and treatment methods remain lacking in clinical practice (Granger and Barnett, 2021). Therefore, delving into the core mechanisms of POCD at the molecular level and identifying new intervention targets represent important directions for current research. In recent years, the role of the mammalian target of rapamycin (mTOR) signaling pathway in cognitive dysfunction has emerged as a research focus (Movahedpour *et al*., 2022; Zheng *et al*., 2021). As a central hub regulating cell growth, autophagy, metabolism and inflammatory responses, its abnormal activation in the nervous system is closely associated with the pathological processes of various cognitive disorders (Yuk *et al*., 2025). More importantly, multiple recent studies have directly confirmed the critical driving role of mTOR in the occurrence of POCD. A recent study demonstrated that in an aged mouse model of orthopedic surgery, hippocampal mTOR signaling is excessively activated, which in turn promotes neuroinflammatory responses and inhibits autophagy, leading to synaptic plasticity impairment and cognitive decline (Chen *et al*., 2024). Another study found that pharmacological inhibition of mTOR activity significantly alleviates hippocampal inflammation induced by surgical trauma and improves cognitive-behavioral performance in mice (Bojja *et al*., 2021). These findings collectively indicate that abnormal activation of the mTOR signaling pathway is a significant and targetable component of POCD pathogenesis. Based on this, we hypothesize that in the specific stress model of partial hepatectomy, the mTOR pathway may similarly play a key role. Therefore, selecting mTOR as the core target for mechanistic exploration in this study is well supported by existing literature and theoretical foundations.

Dexmedetomidine is a highly selective α2-adrenergic

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receptor agonist with multiple pharmacological effects, including sedation, analgesia, antisympathetic and anti-inflammatory actions. Preclinical studies have shown that dexmedetomidine alleviates cognitive impairment in various animal models (Yamazaki *et al*., 2022). However, most of these studies have focused on its ultimate behavioral outcomes or general anti-inflammatory effects. There is currently limited and inconsistent evidence regarding whether it exerts neuroprotective effects by regulating key intracellular signaling pathways such as mTOR. Additionally, some studies suggest that its effects may involve the modulation of autophagy-related pathways (Chen *et al*., 2023). Nevertheless, the relationship between dexmedetomidine and the hippocampal mTOR pathway in a partial hepatectomy-induced POCD model has not yet been systematically investigated.

To address this research gap, the present study sought to answer the following scientific questions: In a rat model of postoperative cognitive dysfunction (POCD) induced by partial hepatectomy, can dexmedetomidine improve cognitive function? Is its effect associated with the regulation of the mTOR signaling pathway in hippocampal tissue? The hypothesis of this study is that dexmedetomidine can alleviate cognitive dysfunction in rats following partial hepatectomy by inhibiting the hippocampal mTOR signaling pathway, thereby reducing downstream neuroinflammation and neuronal apoptosis. To test this hypothesis, we established a rat model of POCD induced by partial hepatectomy and conducted a multi-faceted investigation encompassing behavioral, histopathological and molecular biological analyses. The goal is to provide new experimental evidence to elucidate the neuroprotective mechanisms of dexmedetomidine and to propose novel strategies for the clinical prevention and treatment of POCD.

MATERIALS AND METHODS

Grouping and drug administration of experimental animals

Based on preliminary experimental results, the sample size was calculated using G*Power 3.1 (Kang, 2021), with parameters set at $\alpha = 0.05$, $\beta = 0.2$ and effect size = 0.8. The calculation determined that a minimum of 8 rats per group was required. To ensure robustness, 10 rats were allocated to each group.

Thirty healthy Wistar male rats, aged around 4 months and weighing (220 ± 20) g, were selected from Shanghai Sleiker Laboratory Animal Co., LTD. License No.: SCXK (Shanghai) 2003-2002. Rats were placed in the same environment with free access to food, water and natural light.

A completely randomized design was adopted. After sorting 30 rats by body weight, they were randomly divided into 3 groups using a random number table: the normal group, the model group and the treatment group, with 10 rats in each group. The grouping process was carried out by researchers who did not participate in subsequent experiments to ensure the concealment of allocation. Before the operation, normal saline was used for intervention in the normal group and model group and dexmedetomidine (25 μg/kg, Jiangsu Enhua, H20133331, diluted in normal saline) was administered intraperitoneally 30 min before surgery.

Establishment of POCD rat model after partial hepatectomy

Prior to surgery, rats were fasted for 6 hours with free access to water. Anesthesia was induced via intraperitoneal injection of sodium pentobarbital (40 mg/kg) and additional doses were administered as needed based on pain reflex responses to maintain anesthesia depth *(Xu et al., 2023)*. Anesthesia depth was assessed using a conventional pain reflex test: the skin of the hind limb toe web or tail base was repeatedly pinched with moderate force using surgical forceps. If no significant reflex responses such as limb withdrawal, escape attempts, or head shaking were observed, the rat was considered to have reached a surgical plane of anesthesia. During the procedure, supplemental doses of sodium pentobarbital (10–15 mg/kg, approximately 1/4 to 1/3 of the initial dose) were administered intraperitoneally as needed to maintain a stable anesthetic plane based on the return of reflexes. Respiratory rate and body temperature were continuously monitored using a small-animal physiological monitoring system (PhysioSuite® Series, Kent Scientific Corporation, USA). Body temperature was maintained at 37 ± 0.5°C using a heating pad. After disinfecting the abdominal skin, a midline incision was made to expose the liver. The left lateral lobe was isolated and two ligatures with 4-0 silk sutures were placed at its base. Following blood flow occlusion, the liver lobe was resected. Hemostasis was achieved by gentle pressure with gauze and the abdominal cavity was rinsed with warm saline before being sutured layer by layer. Postoperatively, rats were placed in a warming chamber (30°C) until fully recovered. They were provided with free access to water and soft feed. Additionally, butorphanol (0.05 mg/kg) was administered subcutaneously every 12 hours for 48 hours and gentamicin (5 mg/kg) was injected intramuscularly daily for 3 consecutive days. Morris water maze behavioral testing was conducted on the third day after surgery (Lissner *et al*., 2021). Compared with the sham-operated group, rats in the model group showed significantly prolonged escape latency and a significantly reduced number of platform crossings ($P < 0.05$), indicating impaired spatial learning and memory ability, which met the criteria for a POCD model.

Research methods

Behavioral tests (water maze, shuttle box) and histological evaluations (HE staining, TUNEL count) were conducted

in a double-blind design. Among them, behavioral tests: operated and data recorded by researchers who did not know the groups; Histological score: The section number conceals the grouping information and is independently scored by two pathologists. Molecular detection: The sample numbers of WB and qPCR were randomized and the experimenter did not know the corresponding groups. Only the drug administrator is aware of the treatment group allocation and does not participate in subsequent testing and data analysis.

Acquisition of hippocampus

Three days after the operation, 6 rats from the three groups were randomly selected to receive an appropriate amount of pentobarbital sodium for anesthesia and another 1.5mg/kg of heparinized normal saline was given for treatment. Hippocampal tissue was collected and fixed with paraformaldehyde, then stored at -80ºC for preservation, and later inspected.

HE staining of rat hippocampal tissue to observe its pathological morphological changes

On the third day after surgery, five rats from each group were randomly selected and euthanized by cervical dislocation. Hippocampal tissues were rapidly dissected and immediately immersed in 4% paraformaldehyde fixative (Sigma-Aldrich, Cat No. P6148) for 24 hours at 4°C. The tissues were then dehydrated through a graded ethanol series, cleared in xylene and embedded in paraffin (Leica, Cat No. 14046370013). Continuous sections were cut at a thickness of 4 μm. After deparaffinization in xylene and rehydration through graded ethanol, sections were stained with hematoxylin (Beyotime, Cat No. C0107) for 5 minutes and eosin (Beyotime, Cat No. C0109) for 2 minutes, then mounted with neutral balsam. Evaluation was performed independently by two experienced pathologists using a double-blinded approach. Based on the arrangement of hippocampal neurons, cell morphology, nuclear pyknosis and the degree of vacuolization, a semi-quantitative scoring system was applied (0 points: normal; 1 point: mild damage; 2 points: moderate damage; 3 points: severe damage). The final score for each sample was taken as the average of the two evaluators' scores.

In situ terminal transferase labeling technology (TUNEL)

On the third day after surgery, five rats were randomly selected from each group and euthanized by cervical dislocation *(Wu et al., 2021)*. Hippocampal tissues were rapidly collected, fixed in 4% paraformaldehyde, embedded in paraffin and sectioned at a thickness of 4 μm. After deparaffinization and rehydration, sections were processed for TUNEL staining using the In Situ Cell Death Detection Kit, POD (Roche, Cat. No. 11684817910). Antigen retrieval was performed with proteinase K (20 μg/mL, incubated at 37ºC for 15 min), followed by PBS washes. TUNEL reaction mixture (containing TdT enzyme and fluorescence-labeled dUTP) was added and incubated at 37ºC for 60 min in the dark. After washing three times with PBS (5 min each), sections were stained with DAPI nuclear stain (Beyotime, C1005) at room temperature for 5 min in the dark. Finally, sections were mounted with anti-fade mounting medium and observed under a fluorescence microscope (Nikon Eclipse Ti2). Five non-overlapping fields (×400 magnification) were randomly selected per section. TUNEL-positive cells (green fluorescence) and total DAPI-positive cells were counted. The apoptotic index was calculated as: (number of TUNEL-positive cells / total number of cells) × 100%. All counts were performed independently by two researchers in a double-blinded manner.

Morris water maze experiment

After model establishment, the place navigation test was conducted during the first phase. On the first day, all the selected rats swam freely for 3 minutes. At the beginning of the second day, the rats were divided into two stages, namely morning and afternoon, 4 times/stage, which lasted for 4 days, experienced investigators recorded the time when the rats finally reached the platform. In the second stage, the space search experiment was conducted. On the fifth day, the platform was removed and the same recorder recorded the number of times the rats crossed the platform within 2 minutes. From the 3rd week, all rats were given the shuttle box experiment for 20 times, with an interval of 5s, 5d and 1 time /d. The first 4 days were the training time of rats and the fifth day was the formal training. Record click times (AART), passive avoidance latency (ERL), active avoidance latency (AARL). AART: the difference between the actual number of shocks and the set number of shocks, ERL: the time it took for the rats to be stimulated, AARL: the time it took for the rats to actively avoid the reaction.

The levels of Akt, mTOR, NF-κB, TNF-α protein in hippocampal tissue were determined by western blot assay

An appropriate amount of hippocampal tissue was collected to adjust the protein concentration based on the optical density value of the tissue. First, protein quantification was performed. An appropriate amount of hippocampal tissue was collected from the three groups, and the weight of each group was approximately 70 mg. The hippocampal tissue was homogenized in RIPA lysis buffer (containing 1% PMSF, Beyotime, Cat No. P0013B), then centrifuged at 4ºC (12,000 rpm, 15 min) to collect the supernatant. Protein concentration was determined using the BCA method (Beyotime, Cat No. P0012). Equal amounts of protein (30 μg) were loaded and separated by 10% SDS-PAGE, then transferred onto PVDF membranes (Millipore, Cat No. IPVH00010). The membranes were blocked with 5% skim milk at room temperature for 2 hours and subsequently incubated overnight at 4ºC with primary antibodies under gentle shaking: Akt (CST, #4691, 1:1000), mTOR (CST, #2972, 1:1000), NF-κB p65 (CST, #8242, 1:1000), TNF-α (Abcam, ab6671, 1:800) and β-

actin (CST, #4970, 1:2000). After washing four times with TBST (10 min each), the membranes were incubated with HRP-conjugated secondary antibody (Beyotime, A0208, 1:5000) at room temperature for 2 hours. Following another round of TBST washes, protein bands were visualized using ECL substrate (Beyotime, P0018). Band intensity was quantified using ImageJ software, with β-actin serving as the internal reference for normalization.

Real-time fluorescence quantitative PCR (RQ-PCR) was used to determine the levels of Akt, mTOR, NF-κB p65, TNF-αmRNA in the hippocampus

Hippocampal tissue samples (approximately 30 mg) were collected within 24 hours after the completion of behavioral tests. Total RNA was extracted using the TRIzol method (Invitrogen, Cat No. 15596026) and the A260/A280 ratios were measured (all within the range of 1.8–2.0). For reverse transcription, 1 μg of RNA was processed using the PrimeScript™ RT Reagent Kit (Takara, Cat No. RR047A). The qPCR reaction system consisted of: 10 μL SYBR Premix Ex Taq (Takara, Cat No. RR420A), 0.4 μL each of forward and reverse primers, 2 μL cDNA template and ddH_2O added to a final volume of 20 μL. Reaction conditions were as follows: pre-denaturation at 95°C for 5 min; followed by 40 cycles of 95°C for 15 s and 60°C for 30 s. The relative gene expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method, with β-actin serving as the internal reference gene. Primer sequences and sources are listed in table 1.

Observation indicators

Hippocampal pathological changes, neuronal apoptosis index, cognitive function, Akt, mTOR, NF-κB, TNF-α protein and mRNA levels.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. After confirming normal distribution via the Shapiro–Wilk test, measurement data are expressed as mean ± standard deviation ($\bar{x}$±s). One-way analysis of variance (ANOVA) was used to compare groups. If homogeneity of variance was satisfied (Levene's test, $P > 0.05$), post-hoc pairwise comparisons were performed using the LSD method; if not, Welch's ANOVA followed by Games–Howell post-hoc test was applied. Comparisons between two groups were conducted using an independent samples t-test. All statistical tests were two-tailed and a $P < 0.05$ was considered statistically significant.

RESULTS

Dexmedetomidine improves the pathological morphology of hippocampal tissue and neuronal apoptosis in POCD rats

Under light microscopy, hippocampal neurons in the normal group exhibited intact structures and orderly arrangement. The structure of neurons in the model group was obviously incomplete and the order of each cell was disordered. Hippocampal neuron structure was markedly improved in the treatment group compared with the model group, although it did not fully return to normal levels (Fig. 1). HE staining results (Fig. 1) showed that in the sham-operated group, hippocampal neurons exhibited intact structures and orderly arrangement. In contrast, the model group displayed disordered neuronal arrangement and significant structural damage. The treatment group showed alleviated damage compared to the model group, but did not fully recover to the level of the sham-operated group. TUNEL assay results (Table 2, Fig. 2) revealed that the neuronal apoptosis index in the model group was significantly higher than that in the sham-operated group ($P < 0.001$). The apoptosis index in the treatment group was significantly lower than in the model group ($P < 0.01$) but remained higher than in the sham-operated group ($P < 0.05$), indicating that dexmedetomidine partially inhibits neuronal apoptosis.

Comparison of the cognitive functions of the three groups of rats

The results of the Morris water maze test showed that before modeling, there were no statistically significant differences among the three groups in terms of escape latency or the number of platform crossings ($P > 0.05$). This indicates that all groups had a homogeneous baseline in spatial learning and memory prior to surgical intervention, thereby excluding confounding effects from initial cognitive differences. After modeling, both the model and treatment groups exhibited significantly longer escape latency and fewer platform crossings than the sham-operated group ($P < 0.05$). Following dexmedetomidine treatment, the escape latency in the treatment group was significantly shorter and the number of platform crossings significantly increased compared to the model group ($P < 0.05$). Furthermore, no statistically significant difference was observed between the treatment group and the sham-operated group ($P > 0.05$) (Table 3).

Comparison of levels of Akt, mTOR, NF-κB and TNF-α protein in hippocampal tissues of rats* in *the three groups

The Western blot results (Figs. 3A-C) showed that compared to the sham-operated group, the protein expression of the pro-survival signal Akt was inhibited in the hippocampal tissue of the model group, while the protein levels of mTOR and its downstream pro-inflammatory mediators, NF-κB p65 and TNF-α, were significantly upregulated (Table 4, $P < 0.05$). Dexmedetomidine treatment reversed this abnormal expression pattern: in the treatment group, Akt expression was partially restored, while the protein expression of mTOR, NF-κB p65 and TNF-α was significantly reduced compared to the model group (Fig. 3, Table 4, $P < 0.05$).

Table 1: Sequence of each primer

Index		Primer sequences	Pimer length (bp)
Akt	*Primer-up*	5'-GAGGACGTGGCTATTGTGAAG-3'	105
	PrimerB	5'-TGGACTGAGGAATAGCAGCTC-3'	
mTOR	*Primer-up*	5'-AGTGGAGAGCCTCAACAGGA-3'	126
	PrimerB	5'-TCCAGGGACAGTTTGGATGC-3'	
β-actin	*Primer-up*	5'-CCCATCTATGAGGGTTACGC-3'	350
	PrimerB	5'-TTTAATGTCACGCACGATTTC-3'	
NF-κB p65	*Primer-up*	5'-GACGGCGACTACGACCTGA-3'	102
	PrimerB	5'-TGTCGCTGTCACTGTGGAAG-3'	
TNF-α	*Primer-up*	5'-CAGGCGGTGCCTATGTCTC-3'	78
	PrimerB	5'-CGATCACCCCGAAGTTCAGTAG-3'	

Table 2: Apoptosis of nerve cells in three groups of rats ($\bar{x} \pm s$,%)

Group	n	Nerve cell apoptosis index
Normal group	5	4.98±1.69
Model group	5	16.48±3.56
Treatment group	5	9.84±2.42
F	—	27.921
P	—	0.000

Table 3: Comparison of cognitive function of three groups of rats ($\bar{x} \pm s$).

Group	n	Escape latency period (seconds)			Times of crossing the platform (times)		
		Before modeling	After modeling	After treatment	Before modeling	After modeling	After treatment
Normal group	5	33.67±4.23	32.64±0.65	33.64±0.71	2.81±1.20	0.23±0.82	0.26±0.83
Model group	5	32.57±3.89	74.54±5.73	73.21±4.59	2.54±1.13	1.23±0.21	1.35±0.61
Treatment group	5	32.41±4.15	71.31±5.62	32.49±3.23	2.72±1.32	1.24±0.81	0.23±0.63
F	—	0.141	8.635	8.699	0.064	9.632	10.656
P		0.870	0.000	0.000	0.939	0.000	0.000

Table 4: Comparison of levels of Akt, mTOR, NF-κB, TNF-α protein (relative levels to internal control) in hippocampal tissues of rats in three groups ($\bar{x} \pm s$).

Group	Number of cases	Akt	mTOR	NF-κB	TNF-α
Normal group	5	4.63±0.34	0.36±0.12	0.33±0.02	0.35±0.01
Model group	5	2.36±1.11	2.34±0.23	1.49±0.13	1.61±0.17
Treatment group	5	3.79±1.23	1.65±0.16	0.91±0.13	1.01±0.11
F	—	45.459	215.874	132.478	86.238
P	—	0.000	0.000	0.000	0.000

Table 5: Comparison of the levels of Akt, mTOR, NF-κB, TNF-αmRNA in hippocampal tissue of rats in the three groups ($\bar{x} \pm s$, %).

Group	Number of cases	AktmRNA	mTORmRNA	NF-κBmRNA	TNF-αmRNA
Normal group	5	0.33±0.04	0.36±0.02	0.33±0.02	0.35±0.01
Model group	5	0.76±0.11	0.84±0.13	0.79±0.13	0.81±0.17
Treatment group	5	0.69±0.03	0.45±0.06	0.51±0.03	0.51±0.11
F	—	35.442	24.573	34.421	36.214
P	—	0.000	0.000	0.000	0.000

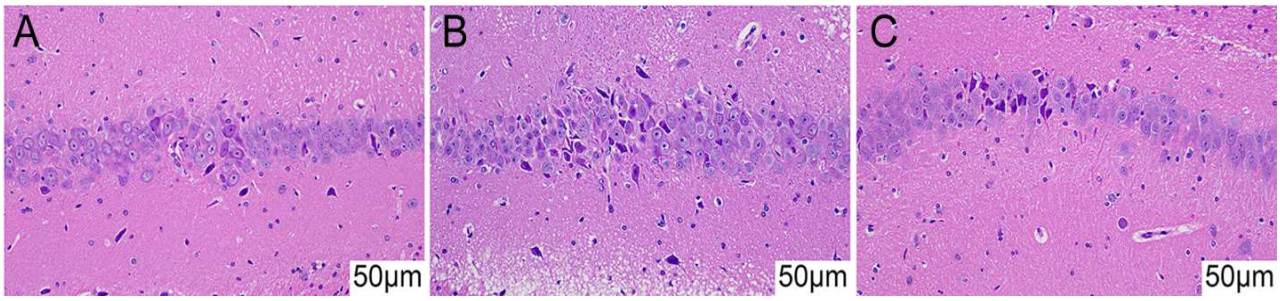

Fig. 1: Morphological comparison of HE staining in hippocampal tissues of rats in each group (×200).
(A) Normal group, the hippocampal neurons are neatly arranged, with clear nuclei and complete structures; (B) Modeling group, disordered arrangement of neurons, cell swelling, and obvious nuclear consolidation suggest severe structural damage; (C) Treatment group, The arrangement of neurons was significantly improved compared with the model group, with less nuclear fixation reduction, but mild vacuolation was still observed.

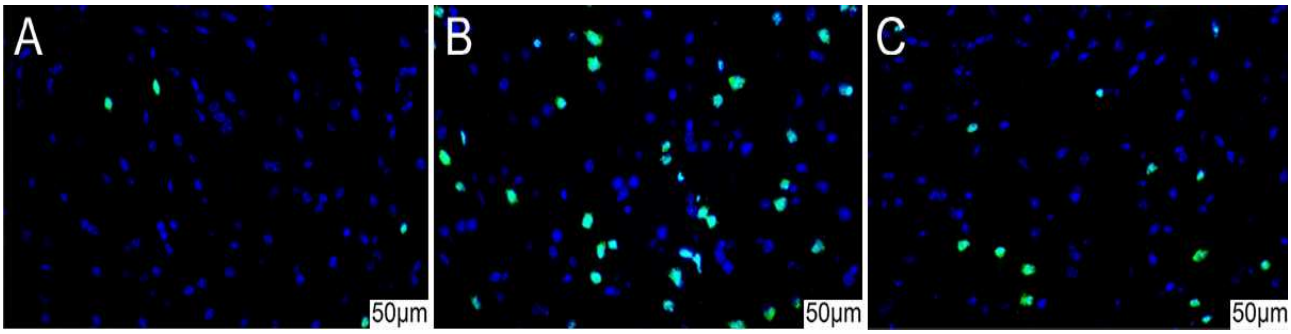

Fig. 2: TUNEL staining was used to detect the apoptosis of hippocampal neurons in the three groups of rats (×400).
(A) Normal group, TUNEL-positive cells were rarely observed; (B) Modeling group, the number of TUNEL-positive cells increased significantly, suggesting active apoptosis; (C) Treatment group, the number of TUNEL-positive cells was significantly reduced compared with that of the Modeling group.

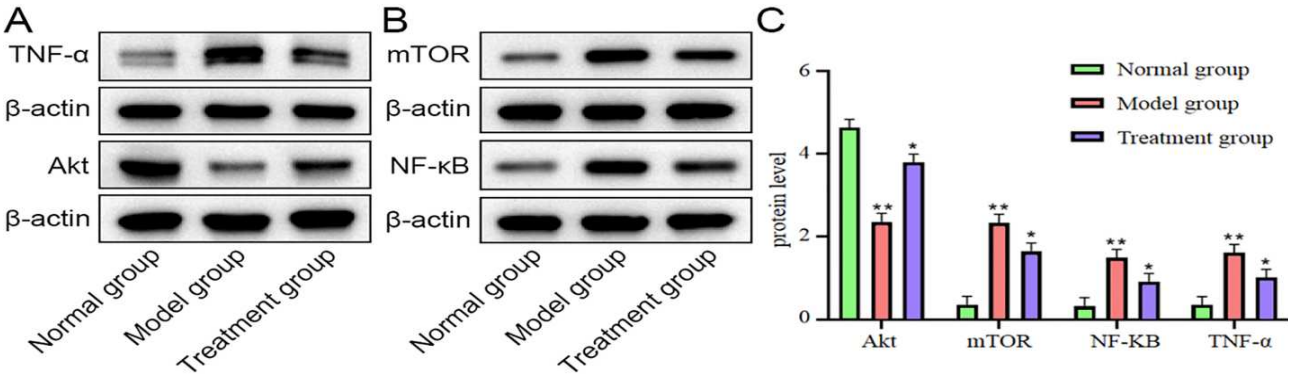

Fig. 3: Western Blot was used to detect the protein expressions of Akt, mTOR, NF-κB and TNF-α in the hippocampal tissues of the three groups of rats
(A) Western Blot was used to detect the protein expressions of TNF-α and Akt in the hippocampal tissues of the three groups of rats; (B) Western Blot was used to detect the protein expressions of mTOR and NF-κB in the hippocampal tissues of the three groups of rats; (C) Quantitative statistical analysis of expression levels of each protein (mean ± standard deviation, n = 5, *P < 0.05, **P < 0.01)

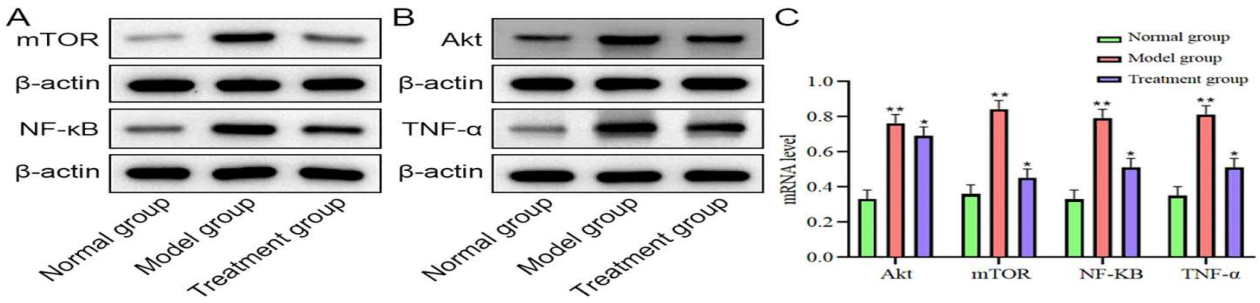

Fig. 4: Real-time fluorescence quantitative PCR was used to detect the mRNA expressions of Akt, mTOR, NF-κB and TNF-α in the hippocampal tissues of the three groups of rats
(A) Western Blot was used to detect the mRNA expressions of mTOR and NF-κB in the hippocampal tissues of the three groups of rats; (B) Western Blot was used to detect the mRNA expressions of Akt and TNF-α in the hippocampal tissues of the three groups of rats; (C) Quantitative statistical analysis of the expression levels of each mRNA (mean ± standard deviation, n = 5, *P < 0.05, **P < 0.01)

Comparison of the levels of Akt, mTOR, NF-κB, TNF-αmRNA in hippocampal tissue of rats in three groups

The qPCR results fully corroborated this trend at the mRNA level (Figs. 4A–C, Table 5). The mRNA expression levels of Akt, mTOR, NF-κB p65 and TNF-α were significantly elevated in the model group ($P < 0.05$ vs. the sham-operated group). In contrast, the mRNA expression of these genes was significantly suppressed in the treatment group ($P < 0.05$ vs. the model group).

DISCUSSION

Postoperative cognitive dysfunction is a common complication following partial hepatectomy. In recent years, the prevention and management of cognitive dysfunction following partial hepatectomy have become a focus of research (Hong *et al*., 2024). To investigate whether the mTOR signaling pathway can serve as a therapeutic target for cognitive dysfunction, this study selected 30 rats for experimentation, aiming to provide insights for the development of novel drugs and improved prevention and treatment strategies for patients with postoperative cognitive dysfunction. This study is the first to demonstrate in a rat model of POCD induced by partial hepatectomy that dexmedetomidine significantly improves hippocampus-dependent cognitive function. This improvement is accompanied by the suppression of key molecules in the mTOR signaling pathway (mTOR, NF-κB, TNF-α) and partial restoration of Akt. Histological evidence further indicates that dexmedetomidine alleviates neuronal structural damage and apoptosis.

The mechanism underlying cognitive dysfunction still needs further study. However, recent studies have confirmed that the pathophysiological processes in rats with POCD primarily involve neuroimmune inflammation and neuronal apoptosis (Sun *et al*., 2022). Most researchers currently agree (Kong *et al*., 2024; Yang *et al*., 2024) that surgical stress triggers the release of A β protein in brain tissue, which destroyed the structure of neurons, further causing damage to the relevant neurons, further cause the body appear oxidative stress and inflammation, thereby contributing to cognitive dysfunction in patients. In this study, the cognitive dysfunction model of rats after partial hepatectomy was established and the hippocampal tissue of rats was stained by HE. The results showed that the structure of hippocampal neurons of rats in the normal group was complete and orderly. The arrangement of neurons in the model group was irregular. The structure of hippocampal neurons in the treatment group was clearly improved, but still did not reach normal levels. The apoptosis index of nerve cells in the three groups was compared. The treatment group data were lower than those of the model group, but there was no significant difference between the treatment and control groups. Moreover, the results of nerve cell apoptosis showed that the arrangement of yellow granules was disordered in the model group, whereas the treatment group showed a clear improvement. It is further confirmed that postoperative cognitive dysfunction may be caused by the destruction of relevant neuron structures in the hippocampus and that dexmedetomidine has a protective effect on postoperative cognitive dysfunction (Jiang et al., 2024; Ye *et al*., 2025). Dexmedetomidine mainly stimulates the α2 receptor and further controls the content of norepinephrine, thereby reducing the amount of neurotransmitters and eventually having a protective effect on the structure of neurons (Zhang *et al*., 2024, Zhang *et al*., 2021).

The findings of this study suggest that the neuroprotective effects of dexmedetomidine may be associated with the inhibition of the hippocampal mTOR signaling pathway. This observation aligns with the recent study by Jiang *et al*. (2020), which demonstrated a close relationship between excessive mTOR activation, hippocampal neuro inflammation and cognitive decline in an aged mouse model of surgical trauma. The present study further validates this association in the specific context of partial hepatectomy, a high-traumatic surgical model. It is hypothesized that dexmedetomidine, as a highly selective

α2-adrenergic receptor agonist, may inhibit sympathetic excitation, reduce catecholamine release and thereby attenuate peripheral and central inflammatory responses (Mei *et al*., 2021). Moreover, it may directly or indirectly modulate the PI3K/Akt/mTOR axis, influencing the nuclear translocation of downstream NF-κB and the synthesis of pro-inflammatory cytokines such as TNF-α. The restorative upregulation of Akt protein observed in this study provides indirect support for this regulatory pathway. Although previous studies have indicated the neuroprotective potential of dexmedetomidine (Zhang *et al*., 2021), its mechanism of action in POCD following partial hepatectomy, particularly its link to the mTOR pathway, remains inadequately elucidated. This study not only demonstrates the efficacy of dexmedetomidine through multi-level behavioral and histological assessments but also connects key molecular nodes such as mTOR, NF-κB, TNF-α and Akt at the molecular level, constructing a preliminary chain of evidence: "dexmedetomidine — inhibition of the mTOR pathway — reduction of neuroinflammation and apoptosis — improvement of cognitive function." However, in contrast to the previous findings (Li *et al*., 2023), the authors reported strong activation of Akt by dexmedetomidine in an ischemic brain injury model, the restoration of Akt observed in this study was limited. This difference may suggest that in the POCD model, the primary targets of dexmedetomidine are more focused on inflammatory processes downstream of mTOR.

In order to further prove that dexmedetomidine can improve the cognitive function of rats, the results of Morris water maze experiment further confirmed that dexmedetomidine has the effect of improving postoperative cognitive dysfunction. The results of this study are consistent with those of previous studies (Li *et al*., 2022, Wang *et al*., 2023).

Meanwhile, this study also has certain limitations. First, the sample size is relatively small, which may not fully account for individual variability. Second, the findings primarily provide correlational evidence, as specific pharmacological tools to manipulate the mTOR pathway—such as rescue or loss-of-function experiments—were not employed; thus, the causal role of this pathway requires further validation. Additionally, the study focused on the hippocampus and did not evaluate other cognition-related brain regions or systemic inflammatory status, leaving the mechanistic landscape incomplete. Moreover, differences exist between animal models and clinical contexts and further clinical studies are needed to determine the optimal dosage, timing and long-term neuroprotective effects of dexmedetomidine. Future work could employ pharmacological or genetic tools to clarify the necessity of the mTOR pathway, extend the observation period to assess long-term outcomes and conduct prospective clinical research to facilitate the translation of basic findings into clinical practice.

CONCLUSION

In summary, this study suggests that dexmedetomidine may alleviate postoperative cognitive dysfunction following hepatectomy by modulating hippocampal mTOR signaling, thereby reducing neuroinflammation and neuronal apoptosis. These findings provide new experimental evidence supporting the exploration of dexmedetomidine as a potential preventive strategy for POCD in clinical settings. Although caution is warranted in translating results from animal studies to humans, this research highlights a promising direction for developing neuroprotective strategies targeting the mTOR pathway.

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None.

Authors' contributions
Xiong Jie: Experimental design, data collection and analysis, manuscript writing; Qing Wang: Experimental implementation and data processing; Licheng Zhang: Research supervision, manuscript revision and review, material provision and technical support. All authors have read and approved the final manuscript.

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Data availability statement
The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval
This study was approved by the Animal Ethics Committee of Huanggang Central Hospital (Approval No.: 20250812). This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Conflict of interest
The authors declare no conflict of interest.

Supplementary data
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