

# Adaptive and regulatory mechanisms in aged rats with postoperative cognitive dysfunction

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## Abstract

Inflammation may play a role in postoperative cognitive dysfunction. 5' Adenosine monophosphate-activated protein kinase, nuclear factor-kappa B, interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$  are involved in inflammation. Therefore, these inflammatory mediators may be involved in postoperative cognitive dysfunction. Western immunoblot analysis revealed 5' adenosine monophosphate-activated protein kinase and nuclear factor-kappa B in the hippocampus of aged rats were increased 1–7 days after splenectomy. Moreover, interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  were upregulated and gradually decreased. Therefore, these inflammatory mediators may participate in the splenectomy model of postoperative cognitive dysfunction in aged rats.

**Key Words:** nerve regeneration; postoperative cognitive dysfunction; splenectomy; brain; aging; 5' adenosine monophosphate-activated protein kinase; nuclear factor-kappa B; tumor necrosis factor- $\alpha$ ; interleukin-1 $\beta$ ; neural regeneration

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## Introduction

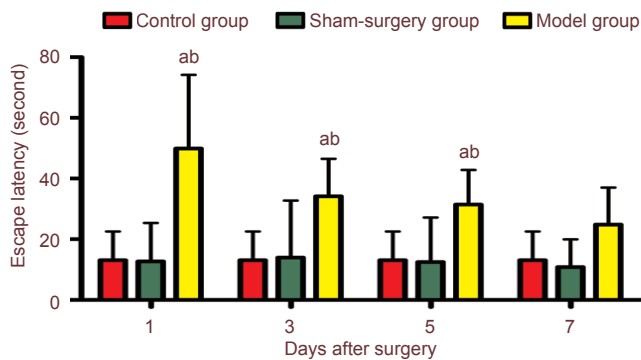
Postoperative cognitive dysfunction has been widely reported to be a common complication following surgery and injury, particularly in elderly patients<sup>[1]</sup>. However, no standard, universally accepted diagnostic criteria exists for this disorder<sup>[2]</sup>. Patients who experience cognitive decline and confusion account for 25–50% of hospitalized patients<sup>[1]</sup>. The influence of surgical procedures on cognition is mainly reflected in learning, language comprehension, executive functioning, thinking, social integration orientation, and memory<sup>[3]</sup>. However, the pathogenic mechanisms of postoperative cognitive dysfunction are unclear. Risk factors for this disorder include advanced age, second surgery, postoperative pain, coexisting diseases, and hospitalization<sup>[4]</sup>. However, advanced age is the most important factor in postoperative cognitive dysfunction. Resisting both injury and repair decreases with increasing age, thus predisposing the elderly to postoperative cognitive dysfunction.

Cognitive dysfunction during and after surgery may be attributed to cerebral ischemia reperfusion, hypoxia, cerebral microemboli and inflammation<sup>[5]</sup>. Cerebral blood flow is normally independent of perfusion pressure in the physiological range. However, cerebral blood flow becomes pressure-dependent when the perfusion pressure is too low or high and consequently increases the susceptibility to ischemia or hyperaemia, respectively owing to the failure in autoregulation of blood flow, which impacts oxygenation, thus leading to cerebral injury<sup>[6]</sup>. Recent studies have shown that postoperative cognitive dysfunction may result from post-surgery inflammation, particularly in the hippocampus<sup>[7-8]</sup>. An inflammatory response is common during sur-

gery- and patient-related factors. Tissue damage causes an inflammatory reaction through the activation of the immune system, which aims to repair the damage. However, this response can also exacerbate the state of tissue damage<sup>[6]</sup>.

Interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  respond to numerous activities in the brain<sup>[7]</sup>. After tibia surgery, mice exhibit hippocampal memory impairment, reactive microglia, and increased levels of interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ <sup>[8-9]</sup>. Pro-inflammatory molecules are promptly released in the circulatory system after tissue damage, surgery, and trauma. For example, tumor necrosis factor- $\alpha$  reaches a peak within minutes after surgery<sup>[10]</sup>. The pro-inflammatory transcription factor, nuclear factor-kappa B, plays a crucial role in the pathophysiology of the central nervous system because it regulates neuroimmune responses, such as the production of pro-inflammatory cytokines<sup>[11]</sup>. Injury, infection or stress activates the central nervous system, increasing the expression of cytokines, chemokines, and adhesion molecules<sup>[11]</sup>. Leukocytes and microglia accumulate and infiltrate the central nervous system<sup>[12]</sup>. Nuclear factor-kappa B can be activated by cytokines, chemokines, and adhesion molecules, and further activates inflammatory cytokines, such as interleukin-1 and tumor necrosis factor- $\alpha$ . Nuclear factor-kappa B controls microglial activation by regulating the transcription of inflammatory mediators. Nuclear factor-kappa B also reduces the inflammation response after brain injury<sup>[13]</sup>.

5' Adenosine monophosphate-activated protein kinase is a protective protein in the central nervous system which is activated by pro- and anti-inflammatory stimuli, such as lipopolysaccharide, ciliary neurotrophic factor, interleukin-10, and transforming growth factor-beta<sup>[14-15]</sup>. Some



**Figure 1 Learning and memory ability is reduced in postoperative cognitive dysfunction rats.**

The escape latency in Morris water maze test was significantly increased 1, 3, and 5 days after surgery in the model group. All data are expressed as mean  $\pm$  SD and were analyzed by one-way analysis of variance followed by the least significant difference test to compare between two groups. <sup>a</sup> $P < 0.05$ , vs. control group; <sup>b</sup> $P < 0.05$ , vs. sham-surgery group.

common pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$ , inhibit the activity of 5' adenosine monophosphate-activated protein kinase by up-regulating the expression of protein phosphatase 2C, which in-turn inhibits 5' adenosine monophosphate-activated protein kinase signaling<sup>[16]</sup>. 5' Adenosine monophosphate-activated protein kinase activation is reduced in interleukin-6 knockout mice<sup>[17]</sup>, indicating that 5' adenosine monophosphate-activated protein kinase activation is dependent on interleukin-6. Furthermore, 5' adenosine monophosphate-activated protein kinase inhibits inflammatory responses in various organs through a wide variety of mechanisms, such as nuclear factor-kappa B<sup>[18]</sup>. In the present study, we investigated the effect of 5' adenosine monophosphate-activated protein kinase, nuclear factor-kappa B, interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$  on postoperative cognitive dysfunction *via* splenectomy in Sprague-Dawley rats by investigating the expression of them in the hippocampus.

## Results

### Quantitative analysis of experimental animals

A total of 90 aged Sprague-Dawley rats (18–22 months) were randomly divided into 3 groups: control (physiological saline) ( $n = 10$ ), sham-surgery (anesthesia only) ( $n = 40$ ), model group (splenectomy model of postoperative cognitive dysfunction) ( $n = 40$ ). After successfully performing the surgery or sham-operation, rats from both groups were divided into four subgroups: 1, 3, 5 or 7 days after surgery ( $n = 10$  per group). Dead rats were supplemented by new rats. All 90 rats were included in the final analysis.

### Learning and memory ability was reduced in postoperative cognitive dysfunction rats

The Morris water maze test showed that spatial learning and memory were damaged after surgery. Escape latencies were significantly ( $P < 0.05$ ) longer at postoperative days 1, 3, and 5 of the model group compared with the control group or the sham-surgery group (Figure 1).

### Expression of 5' adenosine monophosphate-activated protein kinase and inflammatory mediators increased in the hippocampus of postoperative cognitive dysfunction rats

Western blot analysis of hippocampal tissue revealed that

5' adenosine monophosphate-activated protein kinase, nuclear factor-kappa B, interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$  were significantly ( $P < 0.05$ ) increased in postoperative cognitive dysfunction rats compared with the control group or the sham-surgery group (Figures 2, 3). Moreover, the expression of interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  significantly ( $P < 0.05$ ) decreased with increasing postoperative days (Figures 2, 3).

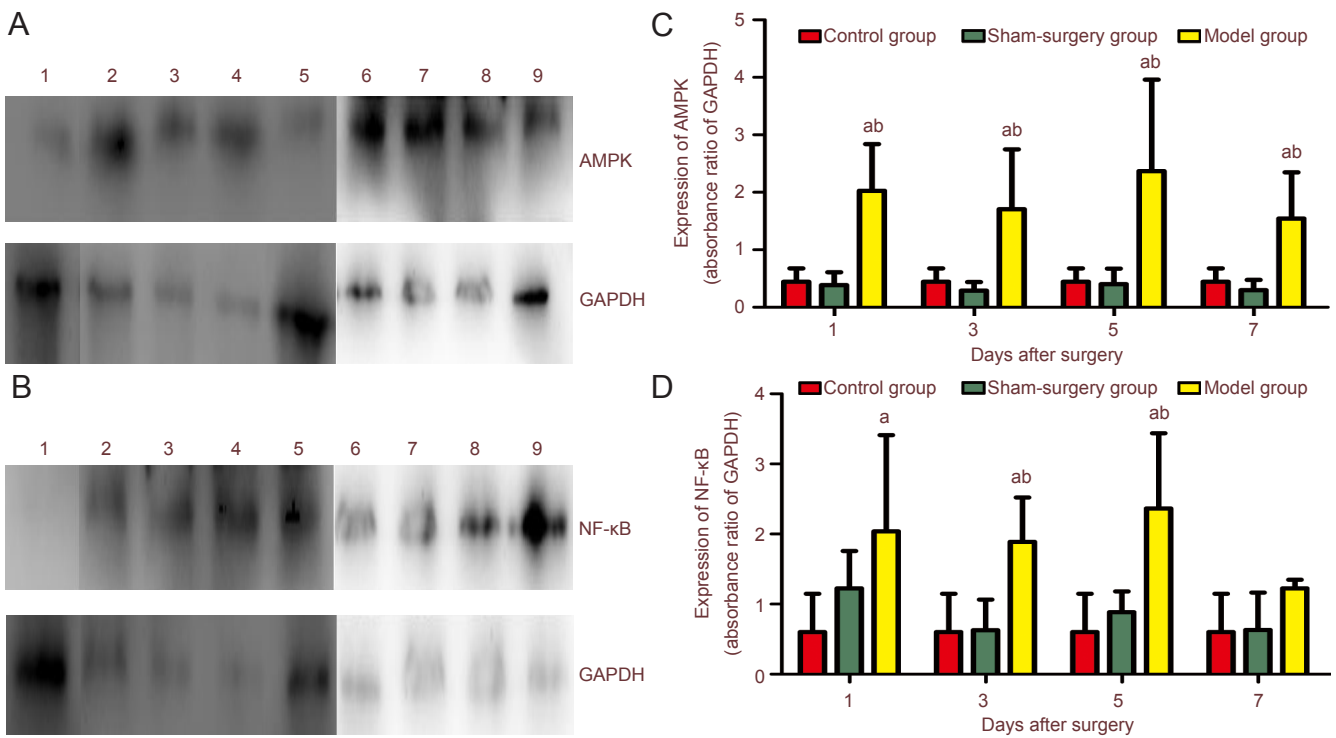
## Discussion

This study indicated that memory and learning declined for a short period in rats after splenectomy. Cognition was impaired 1, 3, and 5 days after splenectomy, and recovery was observed by the 7<sup>th</sup> day. These results suggested that cognition was transiently reduced after splenectomy.

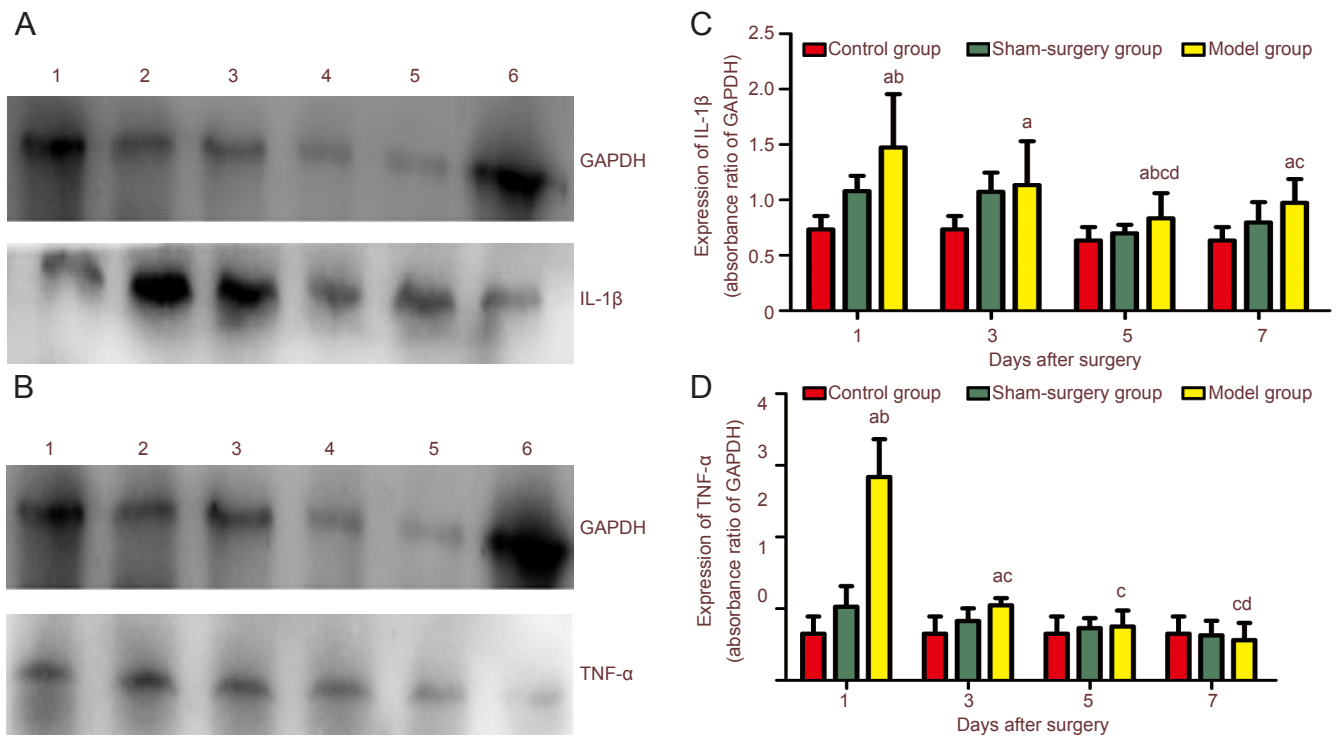
Activated microglia and interleukin-1 $\beta$ -positive microglia are more abundant in the hippocampus of aged mice compared with young mice<sup>[19]</sup>. Therefore, in the present study, aged (18–22 months) Sprague-Dawley rats were chosen to investigate postoperative cognitive dysfunction. Splenectomy has been widely used in past studies<sup>[20-21]</sup>. Splenectomy can be easily performed to establish this model. The recovery time of rats subjected to this surgery is fast, thus results from the Morris water maze task are unaffected<sup>[21]</sup>. The Morris water maze task is a useful tool to determine learning and memory to reflect the severity of injury or the effects of drugs<sup>[22]</sup>.

Furthermore, the expression of 5' adenosine monophosphate-activated protein kinase peaked 5 days after surgery, which may have been caused by inflammation and stress. The expression of inflammatory cytokines and 5' adenosine monophosphate-activated protein kinase increased 1 day after surgery. These results showed that splenectomy induced neuroinflammation and activated 5' adenosine monophosphate-activated protein kinase. Nuclear factor-kappa B, interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$  increased earlier than 5' adenosine monophosphate-activated protein kinase, and moreover, their peak expression occurred earlier. These results suggested that inflammatory cytokines may have activated 5' adenosine monophosphate-activated protein kinase. Peripheral inflammatory cytokines may induce inflammatory responses in the central nervous system through direct and/or indirect ways. Peripheral inflammatory factors can pass through the blood-brain barrier into the central nervous system more easily under surgical and pathological conditions. During injury and surgeries, peripheral inflammatory factors can pass the blood-brain barrier into the central nervous system directly or *via* specific receptors. This effect results in an inflammatory response in the central nervous system<sup>[23]</sup>. Inflammatory cytokines, such as interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor- $\alpha$ , affect neurons and activate astrocytes and microglia<sup>[24]</sup>. Furthermore, cytokines can induce neurotoxicity, which in-turn stimulates astrocytes and microglia in an autocrine and paracrine manner. The subsequent release of inflammatory cytokines aggravates ischemia<sup>[24]</sup> and damages the nervous system. Interleukin-1 $\beta$  is an important mediator in triggering inflammation<sup>[25]</sup>.

Cytokines can pass through the impaired blood-brain barrier and influence cognitive function by affecting neuronal activity and synaptic connections, and causing neurotoxicity and degeneration. Pro-inflammatory cytokines, such as interleukin-1 and tumor necrosis factor- $\alpha$ , have been shown



**Figure 2** The expression of AMPK and NF-κB increased in the hippocampus of postoperative cognitive dysfunction rats. Western blot analysis of AMPK (A, C) and NF-κB (B, D) in the hippocampus of the control, sham-surgery, and model groups at 1, 3, 5, and 7 days after surgery. All data are expressed as mean ± SD and were analyzed by one-way analysis of variance followed by the least significant difference test to compare between two groups. <sup>a</sup>*P* < 0.05, vs. control group; <sup>b</sup>*P* < 0.05, vs. sham-surgery group. 1: Control group; 2–5: sham-surgery group at 1, 3, 5, and 7 days; 6–9: model group at 1, 3, 5, and 7 days; AMPK: 5' adenosine monophosphate-activated protein kinase; NF-κB: nuclear factor-kappa B.



**Figure 3** The expression of IL-1β and TNF-α increased in the hippocampus of postoperative cognitive dysfunction rats. Western blot analysis of IL-1β (A, C) and TNF-α (B, D) in the hippocampus of the control, sham-surgery, and model groups at 1, 3, 5, and 7 days after surgery. All data are expressed as mean ± SD and were analyzed by one-way analysis of variance followed by the least significant difference test to compare between two groups. <sup>a</sup>*P* < 0.05, vs. control group; <sup>b</sup>*P* < 0.05, vs. sham-surgery group; <sup>c</sup>*P* < 0.05, vs. the first day of surgery; <sup>d</sup>*P* < 0.05, vs. the third day of surgery. 1: Control group; 2: sham-surgery group; 3–6: model group at 1, 3, 5, and 7 days; IL-1β: interleukin-1β; TNF-α: tumor necrosis factor-α.

to influence hippocampal-dependent cognition<sup>[26-27]</sup>. The increase in interleukin-6 and other pro-inflammatory cytokines in the hippocampus has been shown to occur in parallel with postoperative cognitive dysfunction in aged rats<sup>[28]</sup>. Moreover, pro-inflammatory cytokines and glial activation may affect postoperative cognitive dysfunction<sup>[28]</sup>. The blood vessels, neural axis and glial cells form the basic unit for brain function. Pro-inflammatory cytokines are produced from glial and neuronal cells, and thus play a role in neuroinflammation. The brain activates inflammatory signaling in response to an immune challenge<sup>[29]</sup>.

Surgical trauma can activate the innate immune system, resulting in strong peripheral inflammation, as seen by the increased levels of interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor- $\alpha$ , and impaired cognitive function<sup>[30-31]</sup>. Nuclear factor-kappa B plays an important role in this process. Nuclear factor-kappa B regulates the expression of a number of genes, many of which regulate inflammation. After surgery, nuclear factor-kappa B is activated by inflammatory factors, cytokines, and calcium overload factors<sup>[32-33]</sup>. Nuclear factor-kappa B activation promotes the expression of inflammatory molecules (such as interleukin-1 $\beta$ , interleukin-6 and tumor necrosis factor- $\alpha$ ) and calcium. An inflammatory cycle response is formed, thus injuring the blood brain barrier and neurons. Overall, nuclear factor-kappa B regulates the expression of tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$ . The balance between these two cytokines is reduced during nervous system injury<sup>[34]</sup>.

Ser/Thr kinase 5' adenosine monophosphate-activated protein kinase reduces energy use and increases energy production *via* glucose and lipid metabolism<sup>[35-36]</sup>. The phosphorylation of tau protein and the accumulation of amyloid in aged people triggers neuronal damage, and may be associated with cognitive dysfunction<sup>[37-39]</sup>. The activation of 5' adenosine monophosphate-activated protein kinase protects the central nervous system by promoting autophagic degradation, regulating tau protein phosphorylation, and reducing amyloidogenesis in neurons<sup>[40-41]</sup>. In various model systems, 5' adenosine monophosphate-activated protein kinase activators, such as 5-aminoimidazole-4-carboxamide 1- $\beta$ -D-ribofuranoside, inhibit inflammatory responses<sup>[42-43]</sup>. 5-Aminoimidazole-4-carboxamide 1- $\beta$ -D-ribofuranoside inhibits inflammation in primary rat microglial cells, and this effect is 5' adenosine monophosphate-activated protein kinase-independent<sup>[44]</sup>. Knockdown of the gene encoding 5' adenosine monophosphate-activated protein kinase or expression of a dominant negative mutant in macrophages promotes a pro-inflammatory state<sup>[45]</sup>. In addition, numerous studies have indicated that activation of 5' adenosine monophosphate-activated protein kinase signaling suppresses nuclear factor-kappa B<sup>[46-48]</sup>. 5' Adenosine monophosphate-activated protein kinase activates silent mating type information regulation 2 homolog-1 and forkhead box O (FOXO) proteins (FOXO3a and FOXO4), which inhibit nuclear factor-kappa B signaling, thereby preventing inflammation<sup>[46-48]</sup>. Therefore, 5' adenosine monophosphate-activated protein kinase can inhibit inflammation through different pathways, which may be one of the mechanisms reducing hippocampal damage.

These downstream proteins also regulate the rate of neuronal survival. Silent mating type information regulation

2 homolog-1 inhibits amyloidogenesis, triggers autophagic degradation, and affects oxidative stress<sup>[48]</sup>. The 5' adenosine monophosphate-activated protein kinase activators, metformin and cilostazol, inhibit tumor necrosis factor- $\alpha$ -induced activation of nuclear factor-kappa B, inhibitor  $\kappa$ -gene binding molecule kinase activity, and tumor necrosis factor- $\alpha$ -induced inhibitor  $\kappa$ -gene binding molecule degradation in humans<sup>[49-50]</sup>. Nuclear factor-kappa B activation is inhibited more in 5' adenosine monophosphate-activated protein kinase-over-expressed cells than cells with kinase-dead 5' adenosine monophosphate-activated protein kinase<sup>[51]</sup>. Overall, 5-aminoimidazole-4-carboxamide 1- $\beta$ -D-ribofuranoside regulates nuclear factor-kappa B by activating 5' adenosine monophosphate-activated protein kinase and phosphorylation of a protein substrate that forms a part of the nuclear factor-kappa B signaling pathway.

Overall, 5' adenosine monophosphate-activated protein kinase and nuclear factor-kappa B may play a role in postoperative cognitive dysfunction in aged rats. Our findings indicated that 5' adenosine monophosphate-activated protein kinase may have been activated by nuclear factor-kappa B, which in-turn inhibited nuclear factor-kappa B expression. The increased expression of 5' adenosine monophosphate-activated protein kinase in rats with postoperative cognitive dysfunction may have indicated that reduced 5' adenosine monophosphate-activated protein kinase activation enhanced the expression. The increased expression of hippocampal interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor- $\alpha$  in post-surgery rats may have indicated that these cytokines played a role in postoperative cognitive dysfunction. In conclusion, splenectomy stimulated the expression of 5' adenosine monophosphate-activated protein kinase, nuclear factor-kappa B, interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$ , and caused postoperative cognitive dysfunction. However, the precise mechanisms of these relationships require further investigation.

## Materials and Methods

### Design

A randomized controlled animal experiment.

### Time and setting

This experiment was performed in the Animal Laboratory of Qingdao Municipal Hospital in China from July to December 2012.

### Materials

A total of 90 clean aged (18–22 months) male Sprague-Dawley rats (480–560 g) were used in this study. Animals were provided by the Dongchuang Animal Science and Technology Service Company (license No. SCXK (Xiang) 2009-0012) (Changsha, Hunan province, China). Animals were housed under a 12-hour light/dark cycle with free access to water and food. All rats acclimatized to their new environment (24–26°C) for 7 days before the commencement of experiments. The transportation and experimental procedures were performed in accordance with the *Guidance Suggestions for the Care and Use of Laboratory Animals*, issued by the Ministry of Science and Technology of China<sup>[52]</sup>. The cages and procedures of transportation were all in accordance with the Association of Business Ethics. This study was approved

by Animal Ethics Committee, Qingdao Municipal Hospital, China.

## Methods

### *Splenectomy*

Chloral hydrate (10%) was injected in the abdominal cavity. The abdominal wall was shaved and disinfected, then a 2–4 cm incision was made in the upper left abdomen through the skin and muscle wall. The spleen was isolated from the surrounding tissue. The blood vessels were ligated by a 3-silk suture, and the spleen was removed. The wound was infiltrated with 1% lidocaine, and then closed with sterile 0-silk sutures. The sham-surgery group only received 10% chloral hydrate. The control group received 0.3 mL/100 g physiological saline.

### *Morris water maze task*

Spatial learning and memory were evaluated in the Morris water maze using a computerized video track system (Xinruan Information Technology Co., Ltd., Shanghai, China) before model establishment. A round pool (120 cm in diameter and 40 cm in height) was divided into four quadrants. A round platform (10 cm in diameter and 30 cm in height) was placed 1 cm below the water surface, located in the center of the southeast quadrant. Both room and water temperatures were maintained between 24 and 26°C. Rats were trained for 5 days with three trials per day (90 seconds at most for a trial and 20 seconds for a rest on the platform before treatment). If the platform was not located within 90 seconds, the automatic recording system was stopped and the rat was guided to the platform artificially and allowed to stay there for approximately 20 seconds. On the 6<sup>th</sup> day, rats were subjected to the model surgery, sham operation or saline injection. The rats were then tested in the Morris water maze 1, 3, 5, and 7 days after treatment, as described above. The time to reach the platform was recorded by video tracking system.

Following the test on 1, 3, 5, and 7 days, rats from the three groups were injected with chloral hydrate and then sacrificed by decapitation. The cerebral cortex was then removed, and the hippocampus immediately dissected<sup>[53]</sup>. The hippocampi were stored in liquid nitrogen for further use.

### *Western blot assay*

Hippocampal homogenates were rapidly solubilized in lysate buffer containing the protease inhibitor (phenylmethylsulfonyl fluoride, and then incubated on ice for 2 hours, followed by centrifugation (12,000 r/min at 4°C for 10 minutes). The supernatant was then extracted, mixed with 1 × sodium dodecyl sulphate buffer, and denatured at 95°C for 5 minutes. Protein samples were separated by 12% sodium dodecyl-sulfate polyacrylamide gel electrophoresis (80 V followed by 100 V). The samples were transferred to polyvinylidene fluoride membranes (60 V for 90 minutes). The membranes were blocked with 5% nonfat milk containing phosphate buffered saline at room temperature for 1 hour. Membranes were incubated with the primary antibodies: rabbit anti-rat 5' adenosine monophosphate-activated protein kinase monoclonal antibody (1:300; Cell Signaling, Boston, MA, USA), rabbit anti-rat nuclear factor- $\kappa$ B monoclonal antibody (1:1,000; Abcam, London, UK), rabbit anti-rat interleukin-1 $\beta$  monoclonal antibody (1:500; Cell Signaling), or rabbit anti-rat tumor necrosis factor- $\alpha$  monoclonal antibody

(1:500; Cell Signaling) for 2 hours at room temperature on a shaking table. Anti-rat glyceraldehyde 3-phosphate dehydrogenase (GAPDH) monoclonal antibody (1:500; Zhongshan Golden Bridge Biotechnology, Beijing, China) as the house-keeping protein. After membranes were washed (three times, 10 minutes each, with PBS containing Tween-20), they were incubated with the secondary antibodies, goat anti-mouse or -rabbit IgG (1:6,000; Zhongshan Golden Bridge Biotechnology) at room temperature for 1 hour. Horseradish-conjugated secondary antibody labeling was detected by enhanced chemiluminescence and blots were exposed with VILBER FUSION FX7 (Beijing Wuzhou Oriental Science and Technology Development Co., Ltd., Beijing, China). The absorbance was normalized to that of GAPDH. Quantitative analysis was performed by Quantity One Software (Bio Rad, Hercules, CA, USA).

### *Statistical analysis*

All data were expressed as mean  $\pm$  SD and were analyzed by one-way analysis of variance followed by the least significant difference test to compare between two groups. All statistical data were analyzed using SPSS 17.0 (SPSS, Chicago, IL, USA). Significance was reached at values of  $P < 0.05$ .

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**Author contributions:** Bi YL was study designer and writer. Liu SY was an experiment and data worker. Yu XJ was statistical data worker. Wang YL and Wang MS conducted the experiment. All authors approved the final version of the manuscript.

**Conflicts of interest:** None declared.

**Peer review:** Postoperative cognitive dysfunction is very common in the clinic. This study used classical models and found that inflammatory factors and AMP-activated protein kinase expression obviously altered in the hippocampus of rats with postoperative cognitive dysfunction and provided an experimental basis for the occurrence of postoperative cognitive dysfunction.

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