doi.org/10.36721/PJPS.2024.37.2.REG.349-356.1

Dexmedetomidine alleviates acute postoperative anxiety in rats by suppressing the NF-κB pathway

Si-Wei Wei, Lei Wu, Zhen Xiang, Er-You Yu and Zhen Du*
Department of Anesthesiology, Hunan Children' Hospital, Changsha City, Hunan, China

Abstract: Evidence suggests that surgical procedures can effect the central nervous system and lead to changes in mood and behavior, rarely understood about the role of acute inflammation in promoting acute anxiety postoperatively. This study was designed to explore the possible mechanism of dexmedetomidine (DEX, a2- adrenergic receptor agonist) for reducing acute postoperative anxiety, which may be related to the activation of nuclear factor kappa B (NF-κB) and downstream signal pathway in the hippocampus. Experiments were conducted with rat, the elevated plus-maze and open field test were performed to evaluate anxiety-like behavior. Inhibit DEX with Atipamezole (AT, α2-adrenergic receptor antagonist) and inhibit NF-κB with Pyrrolidinedithiocarbamate (PDTC, inhibit phosphorylation of IκB, prevent the activation of NF-κB), the level of interleukin-6 (IL-6), IL-1β, IL-10 and Tumor necrosis factor-α (TNF-α); the nuclear translocation of NF-κB in the hippocampus and anxiety-like behavior were measured. Rats exhibited anxiety-like behavior at 6h and 12h after surgery. Preoperative administration of DEX significantly alleviated postoperative anxiety-like behavior. DEX premedication inhibited the nuclear translocation of NF-κB alleviate acute postoperative anxiety. These findings are the first to show that acute postoperative anxiety may be related to NF-κB nuclear translocation in the hippocampus in rats, which can be alleviated by DEX premedication.

Keywords: NF-κB nuclear translocation, acute postoperative anxiety, inflammation, rats, dexmedetomidine.

INTRODUCTION

About 63% of children will experience perioperative anxiety (Lamiani *et al*., 2021). Surgery leads to local tissue damage, physical barrier damage *and* potential environmental and symbiotic microbial exposure, all of which may lead to local inflammation *and* then to a systemic inflammatory response and immunosuppression, while peripheral cytokine signals move to the brain and regulate neuronal activity in specific brain regions, particularly in the hippocampus (Alazawi *et al*., 2016; Ramlawi *et al*., 2006). However, little research appears on the role of acute inflammation in promoting acute anxiety postoperatively.

Inflammation is a key factor in acute and chronic central nervous system (CNS) disorders (Hou *et al*., 2022). It is believed that inflammation mediates important biochemical changes in specific areas of the brain, leading to the anxiety-like behavior (Salim *et al*., 2012). Studies *in vivo* also revealed that the immune system dysregulation had effect on the occurrence of anxiety (Robson *et al*., 2017; Maldonado-Bouchard *et al*., 2016). Hippocampus is implicated structurally and functionally in mood disorders (Michopoulos *et al*., 2015; Aguilera *et al*., 2003). NF-κB, a transcription factor, is expressed ubiquitously and can be activated by inflammatory and stress responses (Rhen *et al*., 2005). A large number of evidence indicates that anxiety behavior can be regulated by NF-κB (Salim *et al*., 2011; Maier *et al*., 1998). Together, these data indicate preliminarily that acute postoperative anxiety is associated with inflammation mediated by NF-κB in the hippocampus.

DEX is a highly specific a2- adrenergic receptor agonist that has numerous applications. Previously, we showed that DEX premedication decreased postoperative anxiety effectively in children (Du *et al*., 2019). Some clinical settings and studies also demonstrated the anti-inflammatory effect of DEX is mediated by the inhibition of NF-κB activation (Zi *et al*., 2019; Kang SH *et al*., 2013). Inhibition of the NF-κB pathway may be the underlying mechanism of the neuroprotective action of DEX (Wang *et al*., 2017). The present study was aimed at investigating whether DEX decrease acute postoperative anxiety through suppressing NF-κB activation in the hippocampus in rats after hernia repair surgery.

MATERIALS AND METHODS

Reagents and *antibodies*

DEX (Hengrui Co., Ltd. Lianyungang, China); rat IL-1β ELISA kit (ke20005, Huamei Bioengineering Co., Ltd. Wuhan, China); rat IL-6 ELISA kit (ke00007, Huamei Bioengineering Co., Ltd.); rat IL-10 ELISA kit (ke00012, Huamei Bioengineering Co., Ltd.); rat TNF-α ELISA kit (ke00068, Huamei Bioengineering Co., Ltd.); p65 (ab16502, Abcam, England); p105 (ab16500, Abcam); proliferating cell nuclear antigen (PCNA, 10205-2-ap, Proteintech, USA); β-actin (60008-1-ig, Proteintech); Pyrrolidinedithiocarbamate (PDTC, S3633, Selleck, USA); Atipamezole (AT, S4650, Selleck, USA).

*Corresponding author: e-mail: hnsetyymzktg@163.com

Animals

Young Sprague-Dawley rats (equal number of males and females, 23–25 days, 60–80 g, Hunan Silaike Jingda Experimental Animal Co., Ltd., China, batch no. 4300470061675) were given food and water. In the first part, rats were randomly divided into seven groups (16 rats per group): 1) Group C: Only saline was intraperitoneally (i.p.) injected without surgery; 2) Group D 6h: DEX (50 μg/kg) was i.p. injected without surgery, behavioral and biochemical changes were measured postoperative 6h; 3) Group D 12h: DEX (50 μg/kg) was i.p. injected without surgery, behavioral and biochemical changes were measured postoperative 12h; 4) Group S 6h : Saline was i.p. injected; surgery was performed 30 mins later, behavioral and biochemical changes were measured postoperative 6h; 5) Group S 12h: Saline was i.p. injected; surgery was performed 30 mins later, behavioral and biochemical changes were measured postoperative 12h; 6) Group D+S 6h: DEX (50 μg/kg) was i.p. injected; surgery was performed 30 mins later, behavioral and biochemical changes were measured postoperative 6h ;7) Group D+S 12h: DEX (50 μg/kg) was i.p. injected; surgery was performed 30 mins later, behavioral and biochemical changes were measured postoperative 12h. In the second part, rats were also randomly divided into five groups (16 rats per group): 1) Group C: Only saline was i.p. injected without surgery; 2) Group S: Saline was i.p. injected, surgery was performed 30 mins later; 3) Group D+S: DEX (50 μg/kg) was i.p. injected, surgery was performed 30 mins later; 4) Group D+S+AT: DEX (50 μg/kg) and AT (250μg/kg) were i.p. injected, surgery was performed 30 mins later; 5) Group S+PDTC: PDTC (100mg/kg) was i.p. injected, surgery was performed 30 mins later. In this part, behavioral and biochemical changes were measured 6h postoperatively.

Hernia repair surgery

Hernia repair surgery was performed 30 min after the i.p. injections. The rats were anesthetized with sevoflurane (5% induction, 2–2.5% maintenance, oxygen flow 3 L/min). The right groin was shaved and disinfected with iodophor *and* a 1.5-cm incision through the skin, fascia *and* muscle was made with a surgical blade. The incision was enlarged with blunt scissors *and* the inguinal tissue was dissociated from the spermatic cord. A thin rubber tube was used to help the spermatic cord separate from the surrounding tissues. All tissues in the spermatic cord except the blood vessels and vas deferens were ligated twice with 2-0 silk thread. The skin was sutured with 4-0 antibacterial suture, pressure was applied to stop the bleeding *and* the wound was cleaned (Bree *et al*., 2015).

Behavioral analysis

All behavioral tests were conducted in the morning in a quiet environment. The researchers who administered the drug did not conduct the test. Thirty minutes before the test, the rats were familiarized with the surrounding environment and testers. To eliminate inter-observer variability, one observer scored each parameter for all rats.

Elevated plus-maze

The elevated plus-maze test is a classic experiment for measuring anxiety behavior (Komada *et al*., 2008). The experimental device is made of wood and include four arms. Two open arms (30cm × 6cm) are surrounded by a small wall made from a 2cm high plastic plate to prevent the rats from falling; two closed arms of the same size perpendicular to the open arm are surrounded by a 15cm high wall. All arms are 40cm above the ground. Same arms are opposite each other *and* there is an square (6cm × 6cm) in the middle of the maze. At the beginning of the experiment, each rat was placed in the square opposite a closed arms *and* was allowed to explore the maze freely for 5 min. The rats' movements were recorded with a digital camera placed directly above the intersection and were scored manually when viewing the video tape. The open arm entries, the time spent in the open arms and the total number of arm entries (i.e., all four arm entries) were analyzed. Anxiety-like behavior was characterized by a decrease in entering and staying in the open arm. The total number of arm entries was a measure of general activity. After each individual test, the device was cleaned and dry completely to prevent subsequent rats from being affected by the odor deposited by the previous rat.

Open field test

The open field test was performed in the same room under the same conditions as the elevated plus-maze test (Dunn *et al*., 2023). The experimental device was a large wooden box (100cm × 100cm) surrounded by a 45cm high wall and in dim light. The square of the wooden space is divided into 16 same squares with white pinstripes. Each rat was placed in the center, facing the same direction all the time. The rats were move freely for 5 min. The digital camera was placed in a high location to record the rats' behavior. The measurements included the time spent in the central area, the frequency of central area entry (four squares in the center) *and* the total distance (represented by the number of crossed lines). The time spent in the central area and the frequency of central area entry are measurements of anxiety behavior, movement distance reflects motor function.

Collection of serum* and *tissues

Following the elevated plus-maze and open field tests, the rats were anesthetized with sevoflurane and decapitated. The blood was collected into 1.5-mL test tubes *and* allowed to coagulate at 4°C for 1h. The sample was centrifuged at 4°C for 15min at 3000 ×*g*, then the supernatant was divided into equal parts and stored at -80°C. Hippocampal tissue was isolated from the brain at 4°C, frozen in liquid nitrogen then stored at -80°C.

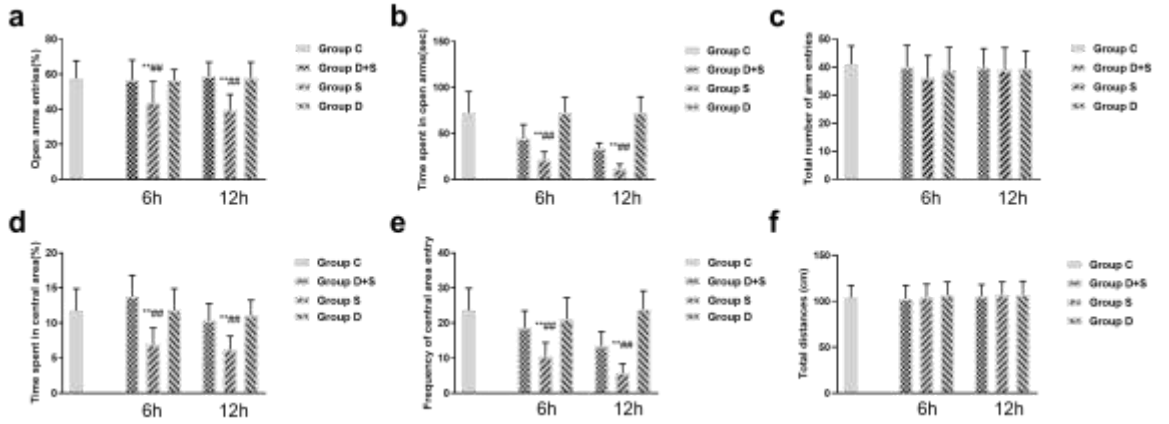

Fig. 1. Effect of DEX premedication on acute anxiety-like behavior after hernia repair surgery in rats. Anxiety-like behavior was tested with the elevated plus-maze and open field test. Open arm entries (%) (a), time spent in the open arm (sec) (b), The total number of arm entries (c), time spent in the central area (%) (d), and frequency of central area entry (e), the total distance travelled (f). Data were presented as the means ± SD; (n=8). Analysis was performed using the univariate analysis of variance (ANOVA) plus Tukey multiple comparison, *P < 0.05, **P < 0.01 VS group C； #P < 0.05, ##P < 0.01 VS group D+S.

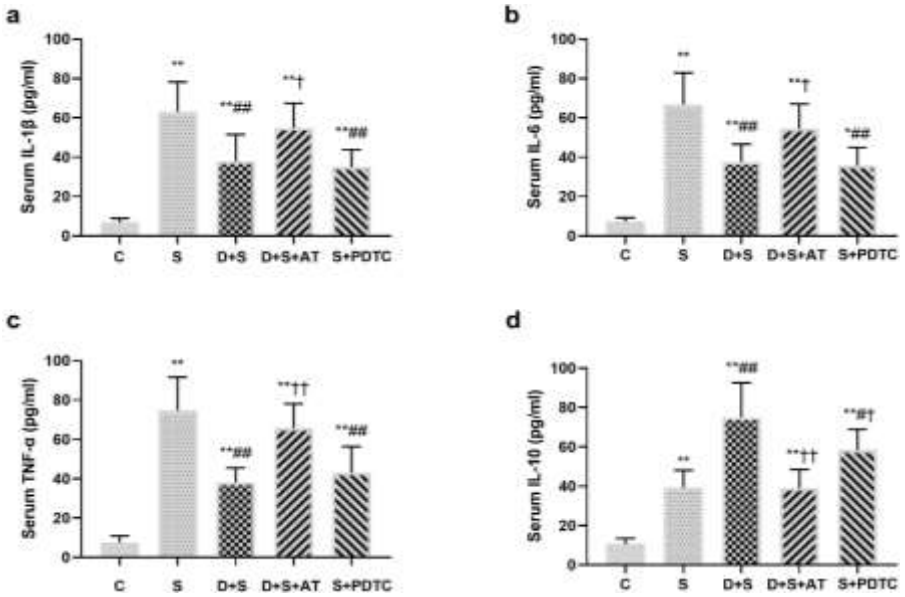

Fig. 2. Effect of dexmedetomidine on peripheral inflammatory response. Serum IL-1β (pg/mL) (a), IL-6 (pg/mL) (b), and TNF-α (pg/mL) (c) IL-10 (pg/mL) (d) were test 6 h postoperative Data were presented as the means ± SD; (n=8). Analysis was performed using the univariate analysis of variance (ANOVA) plus Tukey multiple comparison. *P < 0.05, **P < 0.01 VS group C; #P < 0.05, ##P < 0.01 VS group S; †P < 0.05, ††P < 0.01 VS group D+S.

Enzyme-linked immunosorbent assay

We measured the rat IL-1β, IL-6, IL-10 and TNF-α levels with sandwich ELISA according to the kit instructions.

Western blot analysis

Hippocampal tissue (0.03 g) was minced. Lysis buffer (200 U/L) was added to extract the total protein from the biological samples *and* then cytoplasmic protein and nuclear protein were extracted. We prepared 10% separation glue and added TEMED (*N*, *N*, *N*′, *N*′-tetramethylethylenediamine). Then, loading buffer was added to the cytoplasmic protein and nuclear protein. The foramen primum was injected with 3.5 μL marker *and* 10μL denatured protein was loaded into each blank for electrophoresis. The electrophoresis was run at a constant current of 300 mA for about 84 min for p65, 90 min for p105, 58 min for PCNA *and* 62 min for β-actin. After the transfer of the blots to PVDF membranes, the membrane was incubated with the primary antibody and secondary antibody. Finally, color development was performed.

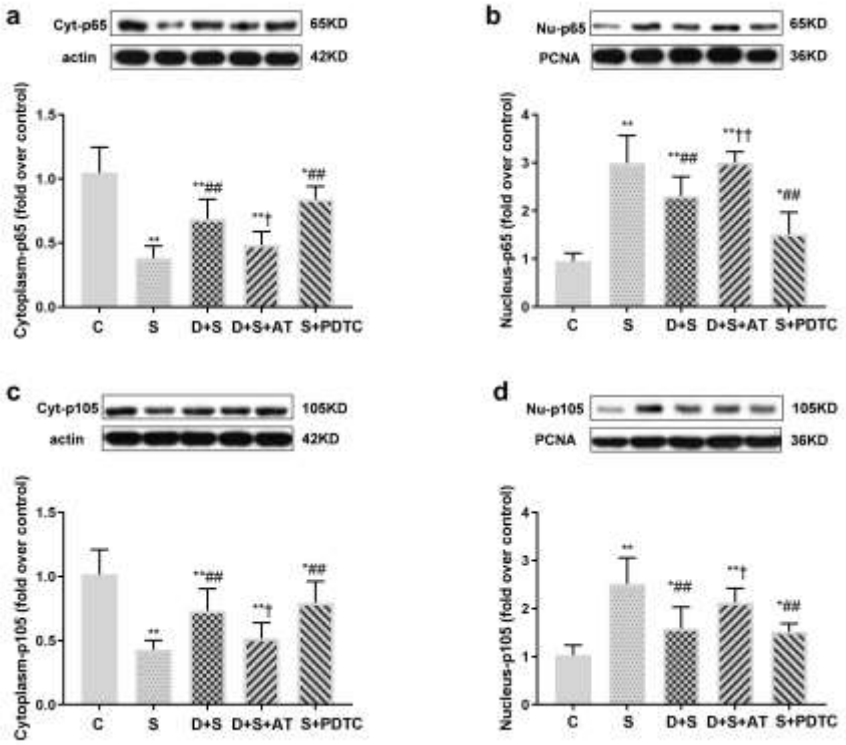

Fig. 3. Effect of dexmedetomidine on NF-κB nuclear translocation in hippocampal. P65 (a) and p105 (c) levels in the hippocampal cytoplasm, p65 (b) and p105 (d) levels in the hippocampal nuclei 6 h postoperative; Data were presented as the means ± SD; (n=8). Analysis was performed using the univariate analysis of variance (ANOVA) plus Tukey multiple comparison. *P < 0.05, **P < 0.01 VS group C; #P < 0.05, ##P < 0.01 VS group S; †P < 0.05, ††P < 0.01 VS group D+S.

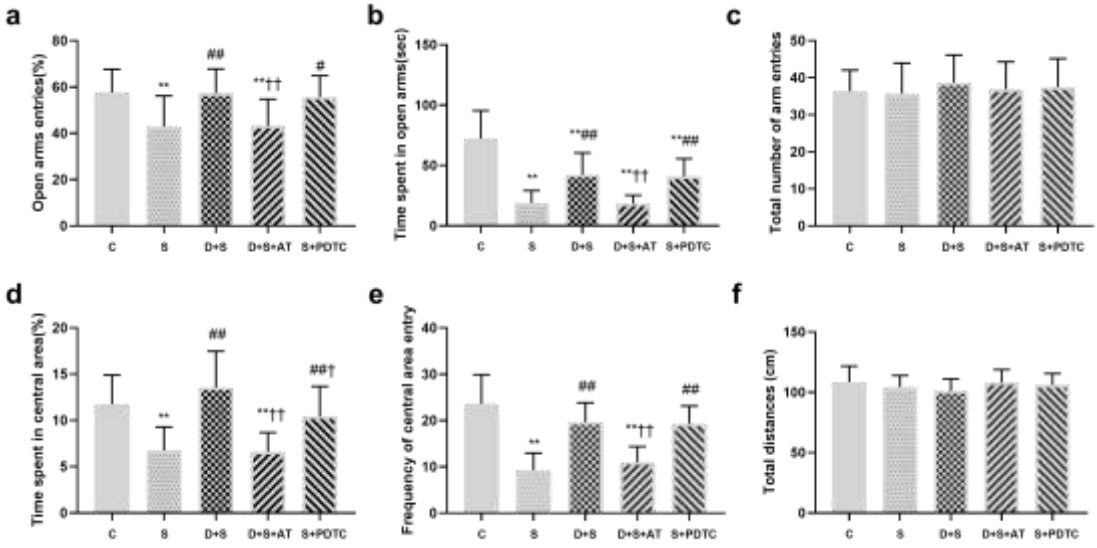

Fig. 4. Effect of NF-κB on acute postoperative anxiety in rats. Anxiety-like behavior was tested with the elevated plus-maze and open field test. Open arm entries (%) (a), time spent in the open arm (sec) (b), The total number of arm entries (c), time spent in the central area (%) (d), and frequency of central area entry (e), the total distance travelled (f). Data were presented as the means ± SD; (n=8). Analysis was performed using the univariate analysis of variance (ANOVA) plus Tukey multiple comparison. *P < 0.05, **P < 0.01 VS group C; #P < 0.05, ##P < 0.01 VS group S; †P < 0.05, ††P < 0.01 VS group D+S.

Ethical approval

The study was carried out after obtaining permission from the Hunan Children's Hospital medical ethics committee (HCHLL-2016-002).

STATISTICAL ANALYSIS

All studies were conducted by an investigator blinded to the treatment. All data are expressed as the mean ± standard deviation (SD). Univariate analysis of variance (ANOVA) plus Tukey multiple comparisons were used for comparison between groups. $P<0.05$ was considered significant. Statistical analysis was performed with SPSS software (version 20.0.0; IBM Corp, Armonk, NY).

RESULTS

Effect of DEX premedication on acute anxiety-like behavior after hernia repair surgery in rats

Anxiety-like behavior was measured by elevated plus-maze and open field test. In the elevated plus-maze, group S6h and S12h spent a shorter time in the open arms ($p<0.01$) and lower percentages of open arm entries ($p<0.01$) compared to the group C; Group D+S 6h and D+S 12h spent a longer time in the open arms ($p<0.01$) and higher percentages of open arm entries ($p<0.01$) than group S6h and S12h (fig. 1a,1b), no significant differences in the total number of arm entries (fig. 1c). In the open field test, group S6h and S12h had lower frequency of central area entry ($p<0.01$) and shorter time spent in the central area ($p<0.01$) compared to group C; Group D+S 6h and D+S 12h had a higher frequency of central area entry ($p<0.01$) and longer time spent in the central area ($p<0.01$) than group S6h and S12h (fig. 1d,1e), no significant differences in the total distance (fig. 1f). And no significant differences in elevated plus-maze and open field test between group C and group D6h and group D12h.

These results suggest that, in rats, inguinal hernia repair surgery results in acute anxiety-like behavior. DEX premedication can significantly alleviate their anxiety-like behavior after surgery. And there were no obvious anxiolytic effects by DEX itself.

Effect of DEX on inflammatory response and NF-κB nuclear translocation in hippocampal

Serum pro-inflammatory and anti-inflammatory cytokines were detected by ELISA. Compared with group C, serum levels of IL-1β ($p<0.01$), IL-6 ($p<0.01$), TNF-α ($p<0.01$) and IL-10 ($p<0.01$) increased 6h postoperative; Compared with group S, group D+S and group S+PDTC had decreased serum IL-1β ($p<0.01$), IL-6 ($p<0.01$) and TNF-α ($p<0.01$) and increased IL-10 ($p<0.01$); Compared with group D+S, group D+S+AT had decreased serum IL-1β ($p=0.0435$), IL-6 ($p=0.0394$) and TNF-α ($p<0.01$) and increased IL-10 ($p<0.01$) (fig. 2).

The changes in NF-κB subunits p65 and p105 in the hippocampal cytoplasm and nucleus were analyzed using western blotting. Compared with group C, p65 ($p<0.01$) and p105 ($p<0.01$) levels in the hippocampal cytoplasm were significantly decreased *and* significantly increased p65 ($p<0.01$) and p105 ($p<0.01$) levels in the hippocampal nuclei 6h postoperative; Compared with group S, group D+S and group S+PDTC had decreased p65 ($p<0.01$) and p105 ($p<0.01$) levels in the hippocampal cytoplasm *and* increased p65 ($p<0.01$) and p105 ($p<0.01$) in the hippocampal nuclei; Compared with group D+S, group D+S+AT had decreased p65 ($p=0.027$) and p105 ($p=0.0315$) levels in the hippocampal cytoplasm *and* increased p65 ($p<0.01$) and p105 ($p=0.0211$) in the hippocampal nuclei (fig. 3).

These results suggest that surgery can induce inflammatory responses in rats. And DEX premedication can significantly reduce the inflammatory responses induced by surgery through NF-κB pathway.

Effect of NF-κB on acute postoperative anxiety in rats

In the elevated plus-maze test, group S and group D+S+AT spent a shorter time in the open arms ($p<0.01$) *and* lower percentages of open arm entries ($p<0.01$) compared to the group C; group D+S spent a longer time in the open arms ($p<0.01$) *and* higher percentages of open arm entries ($p<0.01$) than group D+S+AT; group D+S and group S+PDTC spent a longer time in the open arms ($p<0.01$) and higher percentages of open arm entries ($p<0.01$) than group S (fig. 4a,4b), no significant differences in the total number of arm entries (fig. 4c). In the open field test, group S and group D+S+AT had lower frequency of central area entry ($p<0.01$) and shorter time spent in the central area ($p<0.01$) compared to group C; group D+S had higher frequency of central area entry ($p<0.01$) and longer time spent in the central area ($p<0.01$) than group D+S+AT; group D+S and group S+PDTC had higher frequency of central area entry ($p<0.01$) and longer time spent in the central zone ($p<0.01$) than group S (fig. 4d,4e), no significant differences in the total distance (fig. 4f).

These results suggest that DEX premedication can significantly alleviate acute postoperative anxiety-like behavior by suppressing the NF-κB pathway.

DISCUSSION

The present study, focusing on acute anxiety induced by surgery in an animal model, proves that inflammation induced by NF-κB activation in the hippocampus may promote the development of acute postoperative anxiety, which can be inhibited by DEX premedication.

Anxiety can inhibit the exploratory behavior of rats (Crawley *et al*., 1985). In the present study, rats in the surgery groups showed increased anxiety-like behavior and decreased interest in 6h and 12h postoperatively. DEX premedication significantly reduced the acute postoperative anxiety in rats.

The pathophysiology underlying anxiety is not fully understood. Regulation of the inflammatory response can promote the recovery of neurological function and decreasing anxiety-like behavior, as the IL-1β, IL-6 and TNF-αmay play a key role in negative affects such as anxiety (Wüst *et al*., 2004; Sallinen *et al*., 1997; Pypendop *et al*., 2014; Khandaker *et al*., 2014; Zhang *et al*., 2017). Consistent with these findings, our results showed that the significantly increase of IL-1β, IL-6 and TNF-α, while IL-10 was decreased at 6h postoperatively in the rats. The rats that had undergone surgery showed obvious corresponding anxiety-like behavior. DEX premedication reduced the postoperative inflammatory reaction and alleviated acute postoperative anxiety. These results suggest that acute postoperative anxiety correlates positively with inflammation, at least to a certain extent.

NF-κB as a key role in regulating emotional disorders in the CNS (Cohen *et al*., 2011). Our results demonstrate that surgery induces NF-κB activation in the hippocampus. The accumulation of p105 and p65 promotes the activation of NF-κB (Meffert *et al*., 2005; Mincheva-Tasheva *et al*., 2013). NF-κB activation in the hippocampus can lead to the induction of pro-inflammatory cytokine genes, further increasing the level of pro-inflammatory cytokines in the brain, finally activating the inflammatory response, resulting in inflammation-related acute anxiety (Haftcheshmeh *et al*., 2022; Cheng *et al*., 2017; Rump *et al*., 2022; Koo *et al*., 2010; Mattson *et al*., 2001).

At present, our understanding of postoperative mental and behavioral disorders, including anxiety, is limited *and* postoperative management is still a challenge. Our results indicate that acute postoperative anxiety is associated with neuroinflammation. In a variety of postoperative neurodegenerative diseases, the increases of inflammatory cytokines in the CNS were induced by immune activation *and* leads to symptoms, such as anxiety (Fidalgo *et al*., 2023; Price *et al*., 2014). These findings indicate that targeting inflammatory cytokines and their signaling pathways may be a new strategy for treating postoperative anxiety and other harmful neurological sequelae.

In this study, we found that DEX inhibited the activation of NF-κB in the hippocampus of young Sprague-Dawley rats, thereby decreasing anxiety-like behavior. It is unclear how DEX inhibits NF-κB activation in the hippocampus, although its anti-inflammatory effect may be related to its central sympathetic action and/or cholinergic anti-inflammatory pathway (Zi SF *et al*., 2019; Iovino *et al*., 2020). DEX reduced the initial and subsequent inflammatory cytokine peaks, protecting the host from the excessive systemic consequences of primary injury, which may be an important reason for alleviating acute postoperative anxiety. This explanation may also help us understand why different anesthetics lead to different emotional responses in animal research or clinical practice (Luo *et al*., 2015).

In animal models of systemic inflammatory response syndrome, DEX reduces the severity of neuro inflammation and neuronal apoptosis (Kho *et al*., 2022). After DEX infusion, the incidence of postoperative delirium was reduced by 60% *and* the risk of POCD was reduced by 40% (Su *et al*., 2016; Zhou *et al*., 2016). The results in this study also indicate that the premedication of DEX reversed the effect of the surgery on acute anxiety-like behavior. Our study may expand the existing knowledge of the protective mechanism and clinical application of DEX. Although the application of DEX shows good results, its use in various clinical environments requires further optimization to improve its efficacy and safety.

There are some deficiencies in our research. First, the DEX dosage is 50μg/kg, which has a good anti-inflammatory effect in young Sprague-Dawley rats, while the clinical dosage is 0.5–10μg/kg (Yang *et al*., 2011). Although the application of high-dose DEX (5–15μg/kg) is feasible in the clinic, some risks remain (Linden *et al*., 2005). Studies are needed to determine the optimal concentration of DEX in animals and humans in the future. Second, we only explored the relationship between acute postoperative anxiety and peripheral inflammation and neuroinflammatory reaction 6h and 12h postoperatively. The expression of NF-κB nuclear translocation, inflammatory cytokines *and* postoperative acute anxiety may change with time. Therefore, it is necessary to extend the observation time in future research to further understand the effect of the inflammatory reaction on postoperative anxiety. Third, although pain is one of the important factors influencing postoperative anxiety, we did not observe acute postoperative pain in the rats. Finally, although the hippocampus is one of the key areas of CNS emotion management, the study of biochemical changes in other brain regions may aid the comprehensive assessment of the potential relationship between inflammation and anxiety.

CONCLUSION

In conclusion, our results provide novel evidence that the positive correlation between acute postoperative anxiety and postoperative inflammation which may be related to the activation of NF-κB in the hippocampus. A decrease

in neuroinflammation may be accompanied by a reduction in acute postoperative anxiety.

ACKNOWLEDGMENTS

This work was supported by a grant from Special Fund for Basic Scientifc Research of Hunan Children' Hospital (hospital -level projects, No. B20180310).

REFERENCES

Aguilera IM, Patel D, Meakin GH and Masterson J (2003). Perioperative anxiety and postoperative behavioural disturbances in children undergoing intravenous or inhalation induction of anaesthesia. *Paediatr. Anaesth*., **13**(6): 501-7.

Alazawi W, Pirmadjid N, Lahiri R and Bhattacharya S (2016). Inflammatory and Immune Responses to Surgery and Their Clinical Impact. *Ann. Surg.*, **264**(1): 73-80.

Bree D, Moriarty O, O'Mahony CM, Morris B, Bannerton K, Broom DC, Kelly JP, Roche M and Finn DP (2015). Development and characterization of a novel, anatomically relevant rat model of acute postoperative pain. *J Pain*, **16**(5): 421-35.e1-6.

Cheng P, Wang T, Li W, Muhammad I, Wang H, Sun X, Yang Y, Li J, Xiao T and Zhang X (2017). Baicalin Alleviates Lipopolysaccharide-Induced Liver Inflammation in Chicken by Suppressing TLR4-Mediated NF-kappaB Pathway. *Front Pharmacol*., **8**(3): 547.

Cohen H, Kozlovsky N, Matar MA, Zohar J and Kaplan Z (2011). The characteristic long-term upregulation of hippocampal NF-kappaB complex in PTSD-like behavioral stress response is normalized by high-dose corticosterone and pyrrolidine dithiocarbamate administered immediately after exposure. *Neuropsychopharmacology*, **36**(11): 2286-302.

Crawley JN (1985). Exploratory behavior models of anxiety in mice. *Neurosci. Biobehav. Rev*., **9**(1): 37-44.

Du Z, Zhang XY, Qu SQ, Song ZB, Wei SW, Xiang Z and Guo QL (2019). The comparison of dexmedetomidine and midazolam premedication on postoperative anxiety in children for hernia repair surgery: A randomized controlled trial. *Paediatr. Anaesth*., **29**(8): 843-849.

Dunn AD, Robinson SA, Nwokafor C, Estill M, Ferrante J, Shen L, Lemchi CO, Creus-Muncunill J, Ramirez A, Mengaziol J, Brynildsen JK, Leggas M, Horn J, Ehrlich ME and Blendy JA (2023). Molecular and long-term behavioral consequences of neonatal opioid exposure and withdrawal in mice. *Front. Behav. Neurosci*., **17**(8): 1202099.

Fidalgo AR (2013). Experimental insights into age-exacerbated cognitive dysfunction after peripheral surgery. *Aging Cell*, **12**(3): 523-4.

Haftcheshmeh SM, Abedi M, Mashayekhi K, Mousavi MJ, Navashenaq JG, Mohammadi A and Momtazi-Borojeni AA (2022). Berberine as a natural modulator of inflammatory signaling pathways in the immune system: Focus on NF-kappaB, JAK/STAT *and* MAPK signaling pathways. *Phytother. Res*., **36**(3): 1216-1230.

Hou R, Ye G, Cheng X, Shaw DE, Bakke PS and Caruso M (2023). The role of inflammation in anxiety and depression in the European U-BIOPRED asthma cohorts. *Brain. Behav. Immun*., **111**(6): 249-258.

Iovino M, Messana T, De Pergola G, Iovino E, Guastamacchia E, Licchelli B, Vanacore A, Giagulli VA and Triggiani V (2020). Brain Angiotensinergic Regulation of the Immune System: Implications for Cardiovascular and Neuroendocrine Responses. *Endocr. Metab. Immune. Disord. Drug. Targets*, **20**(1): 15-24.

Kang SH, Kim YS, Hong TH, Chae MS, Cho ML, Her YM and Lee J (2013). Effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. *Acta. Anaesthesiol. Scand*., **57**(4): 480-7.

Khandaker GM, Pearson RM, Zammit S, Lewis G and Jones PB (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA. Psychiatry*, **71**(10): 1121-8.

Kho W, von Haefen C, Paeschke N, Nasser F, Endesfelder S, Sifringer M, Gonzalez-Lopez A, Lanzke N and Spies CD (2022). Dexmedetomidine Restores Autophagic Flux, Modulates Associated microRNAs and the Cholinergic Anti-inflammatory Pathway upon LPS-Treatment in Rats. *J. Neuroimmune. Pharmacol*., **17**(1-2): 261-276.

Komada M, Takao K and Miyakawa T (2008). Elevated plus maze for mice. *J. Vis. Exp*., **22**(5): 1088.

Koo JW, Russo SJ, Ferguson D, Nestler EJ and Duman RS (2010). Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. *Proc. Natl. Acad. Sci USA*., **107**(6): 2669-74.

Lamiani G, Bonazza F, Del NS and Meyer EC (2021). The impact of visiting the Intensive Care Unit on children's and adolescents' psychological well-being: A systematic review. *Intensive Crit. Care. Nurs*., **65**(3): 103036.

Linden A, Laan M and erson GP (2005). Neutrophils, interleukin-17A and lung disease. *Eur. Respir. J*., **25**(1): 159-72.

Luo C, Zhang YL, Luo W, Zhou FH, Li CQ, Xu JM and Dai RP (2015). Differential effects of general anesthetics on anxiety-like behavior in formalin-induced pain: Involvement of ERK activation in the anterior cingulate cortex. *Psychopharmacology (Berl*), **232**(24): 4433-44.

Maier SF and Watkins LR (1998). Cytokines for psychologists: implications of bidirectional immune-to-

brain communication for understanding behavior, mood *and* cognition. *Psychol. Rev*., **105**(1): 83-107.

Maldonado-Bouchard S, Peters K, Woller SA, Madahian B, Faghihi U, Patel S, Bake S and Hook MA (2016). Inflammation is increased with anxiety- and depression-like signs in a rat model of spinal cord injury. *Brain. Behav. Immun*., **51**(9): 176-195.

Mattson MP and Camandola S (2001). NF-kappaB in neuronal plasticity and neurodegenerative disorders. *J. Clin. Invest*., **107**(3): 247-54.

Meffert MK and Baltimore D (2005). Physiological functions for brain NF-kappaB. *Trends. Neurosci*., **28**(1): 37-43.

Michopoulos V and Jovanovic T (2015). Chronic inflammation: A new therapeutic target for post-traumatic stress disorder?, *Lancet Psychiatry*, **2**(11): 954-5.

Mincheva-Tasheva S and Soler RM (2013). NF-kappaB signaling pathways: Role in nervous system physiology and pathology. *Neuroscientist*, **19**(2): 175-94.

Price CC, Tanner JJ, Schmalfuss I, Garvan CW, Gearen P, Dickey D, Heilman K, McDonagh DL, Libon D, Leonard C, Bowers D and Monk TG (2014). A pilot study evaluating presurgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroplasty in older adults. *Anesthesiology*, **120**(3): 601-13.

Pypendop BH and Ilkiw JE (2014). Pharmacokinetics of dexmedetomidine after intravenous administration of a bolus to cats. *Am. J. Ve.t Res*., **75**(5): 441-5.

Ramlawi B, Rudolph JL, Mieno S, Feng J, Boodhwani M, Khabbaz K, Levkoff SE , Marcantonio, ER , Bianchi C and Sellke FW (2006). C-Reactive protein and inflammatory response associated to neurocognitive decline following cardiac surgery. *Surgery*, **140**(2): 221-6.

Rhen T and Cidlowski JA (2005). Anti-inflammatory action of glucocorticoids--new mechanisms for old drugs. *N. Engl. J. Med*., **353**(16): 1711-23.

Robson MJ, Quinlan MA and Blakely RD (2017). Immune System Activation and Depression: Roles of Serotonin in the Central Nervous System and Periphery. ACS. *Chem. Neurosci*, **8**(5): 932-942.

Rump K and Adamzik M (2022). Epigenetic Mechanisms of Postoperative Cognitive Impairment Induced by Anesthesia and Neuroinflammation. *Cells*, **11**(19): 2954.

Salim S, Asghar M, Taneja M, Hovatta I, Chugh G, Vollert C and Vu A (2011) Potential contribution of oxidative stress and inflammation to anxiety and hypertension. *Brain Res*., **1404**(2): 63-71.

Sallinen J, Link RE, Haapalinna A, Viitamaa T, Kulatunga M, Sjoholm B, Macdonald E, Pelto-Huikko M, Leino T, Barsh GS, Kobilka BK and Scheinin M (1997). Genetic alteration of alpha 2C-adrenoceptor expression in mice: influence on locomotor, hypothermic and neurochemical effects of dexmedetomidine, a subtype-nonselective alpha 2-adrenoceptor agonist. *Mol. Pharmacol*., **51**(1): 36-46.

Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M and Ma D (2016). Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet*, **388**(10054): 1893-1902.

Wang L, Liu H, Zhang L, Wang G, Zhang M and Yu Y (2017). Neuroprotection of Dexmedetomidine against Cerebral Ischemia-Reperfusion Injury in Rats: Involved in Inhibition of NF-kappaB and Inflammation Response. *Biomol Ther (Seoul*), **25**(4): 383-389.

Wüst S, Federenko IS, van Rossum EF, Koper JW, Kumsta R, Entringer S and Hellhammer DH (2004). A psychobiological perspective on genetic determinants of hypothalamus-pituitary-adrenal axis activity. *Ann. NY. Acad. Sci*., **1032**(7): 52-62.

Yang CL, Chen CH, Tsai PS, Wang TY and Huang CJ (2011). Protective effects of dexmedetomidine-ketamine combination against ventilator-induced lung injury in endotoxemia rats. *J Surg Res*., **167**(2): e273-81.

Zhang Q, Zhang J, Yan Y, Zhang P, Zhang W and Xia R (2017). Proinflammatory cytokines correlate with early exercise attenuating anxiety-like behavior after cerebral ischemia. *Brain Behav*., **7**(11): e00854.

Zhou C, Zhu Y, Liu Z and Ruan L (2016). Effect of dexmedetomidine on postoperative cognitive dysfunction in elderly patients after general anaesthesia: A meta-analysis. *J. Int. Med. Res*., **44**(6): 1182-1190.

Zi SF, Li JH, Liu L, Deng C, Ao X, Chen DD and Wu SZ (2019). Dexmedetomidine-mediated protection against septic liver injury depends on TLR4/MyD88/NF-kappa B signaling down regulation partly via cholinergic anti-inflammatory mechanisms. *Int. Immunopharmacol*, **76**(5): 105898.