Research Paper

Mechanism of Dexmedetomidine in Alleviating the Propofol Induced Hippocampal Neurons Destruction in Developing Rats

YUEE LIU, JUNER GUO[1], Y. GUO[2], XUEMEI ZHANG[3]* AND JIANZHONG GAO

Department of Anesthesiology, Shanxi Province Fenyang Hospital, [1]Department of Ophthalmology, Shanxi Fenyang Aier Ophthalmology Hospital, [2]Department of Nursing, Fenyang College of Shanxi Medical University, [3]Department of Anesthesiology, Shanxi Province Fenyang Hospital, Fenyang, Shanxi Province 032200, China

To investigate the mechanism of dexmedetomidine in alleviating the propofol induced hippocampal neurons destruction in developing rats. 189 healthy specific pathogen-free rats of 10 d old were divided into 9 groups by random number table method, namely, group N, group F, group D, group P, PD_{25} group, PD_{50} group, PD_{75} group, LYPD group and TDPD group, each with 21 cases. Then various indexes were observed, including general conditions, blood gas analysis, the messenger ribonucleic acid expression levels of phosphoinositide 3-kinase, protein kinase B and glycogen synthase kinase 3 beta, the protein expression levels of protein kinase B, glycogen synthase kinase 3 beta, phospho protein kinase B (ser473) and phospho glycogen synthase kinase 3 beta (ser9) in hippocampus, as well as ultrastructure of hippocampal neurons. 1 h after the consciousness recovery, the body weight, pH value, pressure of inhaled oxygen, partial pressure carbon dioxide, arterial oxygen saturation, bicarbonate and base excess had no difference among these groups ($p<0.05$). The phospho protein kinase B (ser473)/protein kinase B of PD_{75} group and TDPD group as well as the p glycogen synthase kinase 3 beta (ser9)/glycogen synthase kinase 3 beta in PD_{25} group, PD_{50} group, PD75 group, LYPD group and TDPD group were higher than those of group P ($p<0.05$). The phospho protein kinase B (ser473)/protein kinase B and phospho glycogen synthase kinase 3 beta (ser9)/glycogen synthase kinase 3 beta in LYPD group were lower than those of the PD_{75} group ($p<0.05$), while the p protein kinase B (ser473)/protein kinase B and p glycogen synthase kinase 3 beta (ser9)/glycogen synthase kinase 3 beta in TDPD group were higher than those of the PD_{75} group ($p<0.05$). Propofol anesthesia can cause damage to hippocampal neurons in developing rats; neuroprotection effect of dexmedetomidine may be related to activation of phosphoinositide 3-kinase/protein kinase B/glycogen synthase kinase 3 beta signal pathway.

Key words: Dexmedetomidine, propofol, rat hippocampal neurons, protein kinase B, apoptosis

Propofol is a short-acting intravenous anesthetic with rapid onset, short duration of action, and quick recovery. It is widely used in clinical settings for inducing and maintaining anesthesia during complex surgical procedures, as well as for anesthesia during outpatient procedures like gastroscopy and colonoscopy[1,2]. Numerous studies have shown that propofol exhibits neurotoxicity to hippocampal neurons in developing mammals, promoting neuronal apoptosis or necrosis, reducing dendritic spine density and causing long-term cognitive impairment. However, the specific mechanisms behind these effects are not yet clear[3,4]. Dexmedetomidine is a highly selective and specific Alpha (α) 2-adrenergic receptor agonist. As a safe and effective anesthetic adjuvant, dexmedetomidine can reverse the inhibitory effect of propofol on hippocampal neuron cell viability and reduce the neurotoxicity of propofol[5,6]. Phosphoinositide 3-kinase/Protein Kinase B (PI3K/Akt) is a survival signaling pathway widely present

Accepted 04 September 2023
Revised 05 November 2022
Received 22 December 2021
Indian J Pharm Sci 2023;85(5):1234-1240

***Address for correspondence**
E-mail: 15835809584@163.com

in various nerve cells, and it plays a crucial role in transducing membrane receptor signals into the cell. In this study, we investigated the impact of dexmedetomidine on the PI3K/Akt signaling pathway in the hippocampus of developing rats anesthetized with propofol, aiming to explore the molecular mechanism through which dexmedetomidine mitigates propofol-induced damage to hippocampal neurons.

MATERIAL AND METHODS

Experimental animals and grouping:

A total of 189 healthy Specific Pathogen-Free (SPF) grade rats aged 10 d, each weighing 12-18 g, were obtained from Nanjing Lambda Pharmaceutical Co., Ltd. (License No.: SYXK (Su) 2017-0040). The rats were housed in individual ventilated cages in an animal laboratory with a temperature maintained at 22°-25° and humidity at 50 %-60 %, with a 12 h light-dark cycle. All rats were provided with sterile feed and unrestricted access to water. Prior to the experiments, the rats were fasted for 12 h. The rats were randomly divided into nine groups, with 21 rats in each group: Normal saline group (N group, n=21), fat emulsion group (F group, n=21), dimethyl sulfoxide group (D group, n=21), propofol 100 mg/kg group (P group, n=21), propofol 100 mg/kg+dexmedetomidine 25 μg/kg group (PD_{25} group, n=21), propofol 100 mg/kg+dexmedetomidine 50 μg/kg group (PD_{50} group, n=21), propofol 100 mg/kg+dexmedetomidine 75 μg/kg group (PD_{75} group, n=21), LY294002 25 μg+dexmedetomidine 75 μg/kg+propofol 100 mg/kg group (LYPD group, n=21), and TDZD-8 1 mg/kg+dexmedetomidine 75 μg/kg+propofol 100 mg/kg group (TDPD group, n=21). There were no significant differences in general characteristics among the three groups of rats. The study was approved by the animal protection association and the medical ethics committee.

Experimental drugs and reagents:

Dexmedetomidine (Jiangsu Enhua Pharmaceutical Co., Ltd.); propofol (Hebei Yipin Pharmaceutical Co., Ltd.); dimethyl sulfoxide (Hunan Yunbang Biomedical Co., Ltd.); LY294002 (Nanjing Sanshu Biological Technology Co., Ltd.); Reverse Transcription (RT) kit (Shanghai Pushen Biotechnology Co., Ltd.); Phosphate-Buffered Saline (PBS) (Shanghai Huiying Biotechnology Co., Ltd.); total Ribonucleic Acid (RNA) extraction kit (Shanghai Sixin Biotechnology Co., Ltd.); 10 % paraformaldehyde (Shanghai Yuanye Biotechnology Co., Ltd.); Trizol reagent (Hangzhou Xinjing Biotechnology Co., Ltd.); PI3K primers (Beijing Bosen Biotechnology Co., Ltd.); Akt primers (Nanjing Saihongrui Biological Technology Co., Ltd.); Glycogen Synthase Kinase-3 beta (GSK-3β) primers (Shanghai Yubo Biotechnology Co., Ltd.); Radioimmunoprecipitation Assay (RIPA) lysis buffer (Shanghai Nuolun Biomedical Technology Co., Ltd.); phosphatase inhibitor (Shenzhen Kangchuyuan Co., Ltd.); rabbit anti-human Akt monoclonal antibody (Wuhan Aibotaike Biological Technology Co., Ltd.); rabbit anti-human pAkt (ser473) monoclonal antibody (Beijing Baiolaibo Technology Co., Ltd.); rabbit anti-human GSK-3β monoclonal antibody (Shanghai Yanjing Biotechnology Co., Ltd.) and rabbit anti-human pGSK-3β (ser9) monoclonal antibody (Wuhan Aibotaike Biological Technology Co., Ltd.).

Preparation of the experimental model:

N group and F group: Intraperitoneal injection of 100 mg/kg normal saline or fat emulsion, respectively.

D group: Intracerebroventricular injection of 5 μl 10 % dimethyl sulfoxide.

P group: Intraperitoneal injection of 50 mg/kg propofol, followed by an additional 50 mg/kg propofol when the rat showed a physical response.

PD_{25}, PD_{50} and PD_{75} groups: Intraperitoneal injection of 25 μg/kg, 50 μg/kg, or 75 μg/kg dexmedetomidine, respectively, followed by intraperitoneal injection of 50 mg/kg propofol 30 min later and an additional 50 mg/kg propofol when the rat regained the righting reflex.

LYPD group: Intracerebroventricular injection of 25 μg/5 μl LY294002, followed by intraperitoneal injection of 75 μg/kg dexmedetomidine 30 min later, and then intraperitoneal injection of 50 mg/kg propofol 30 min later, and an additional 50 mg/kg propofol when the rat regained the righting reflex.

TDPD group: Intraperitoneal injection of 1 mg/kg TDZD-8, followed by intraperitoneal injection of 75 μg/kg dexmedetomidine 30 min later, and then intraperitoneal injection of 50 mg/kg propofol 30 min later, and an additional 50 mg/kg propofol when the rat regained the righting reflex.

Experimental methods:

Blood gas analysis: After the rats woke up from anesthesia, blood gas analysis was performed to

measure pH value, Partial pressure of Oxygen (PaO_2), Partial pressure of Carbon dioxide ($PaCO_2$), arterial Oxygen Saturation (SaO_2), Bicarbonate (HCO_3), and Base Excess (BE).

RT-Polymerase Chain Reaction (RT-PCR): RT-PCR was used to detect the expression of PI3K, messenger RNA (mRNA), Akt mRNA and GSK-3β mRNA in hippocampal tissues.

Western blot: Western blot was performed to detect the expression of Akt, GSK-3β, pAkt (ser473) and pGSK-3β (ser9) proteins in hippocampal tissues.

Transmission electron microscopy observation: Transmission electron microscopy was used to observe the ultrastructure of hippocampal neurons, including neuronal cell nuclei, mitochondria and synapses.

Observation indices:

General characteristics and blood gas analysis of the nine rat groups, expression levels of PI3K mRNA, Akt mRNA and GSK-3β mRNA in hippocampal tissues of the nine rat groups, expression levels of Akt, GSK-3β, pAkt (ser473) and pGSK-3β (ser9) proteins in hippocampal tissues of the nine rat groups and ultrastructure of hippocampal neurons in the nine rat groups.

Statistical analysis:

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 23.0 software. Data were presented as mean±standard deviation. One-way Analysis of Variance (ANOVA) was used for comparisons, and the Student–Newman–Keuls (SNK)-q test was used for pairwise comparisons. A $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

There were no significant differences in body weight, pH value, PaO_2, $PaCO_2$, SaO_2, HCO_3, and BE among the nine rat groups ($p>0.05$), as shown in Table 1.

RT-PCR results showed that there were no significant differences in the expression levels of PI3K mRNA, Akt mRNA and GSK-3βmRNA between the F group and D group compared to the N group ($p>0.05$). However, the expression of GSK-3β, mRNA in the P group was significantly higher than that in the N group ($p<0.05$), while the expression levels of PI3K mRNA and Akt mRNA in the LYPD group, as well as GSK-3β mRNA in the TDPD group, were significantly lower than those in the N group ($p<0.05$). Moreover, there were no significant differences in the expression levels of PI3K mRNA and Akt mRNA between the PD_{25}, PD_{50}, PD_{75} and TDPD groups compared to the P group ($p>0.05$), while the expression levels of PI3K mRNA and Akt mRNA in the LYPD group, as well as GSK-3β mRNA in the PD_{75} and TDPD groups, were significantly lower than those in the P group ($p<0.05$) as shown in Table 2.

TABLE 1: GENERAL SITUATION AND BLOOD GAS ANALYSIS OF 9 GROUPS OF RATS (n=21, $\bar{x}\pm s$)

Group	Weight (g)	pH value	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	SaO_2 (%)	HCO_3 (mmol/l)	BE (mEq/l)
N	12.51±1.52	7.30±0.03	92.62±5.61	44.25±4.51	92.91±1.32	23.72±2.45	-2.3±1.31
F	11.44±1.91	7.30±0.02	91.43±7.94	44.92±4.71	92.83±2.62	23.77±2.91	-1.9±1.34
D	12.45±1.42	7.30±0.02	91.83±5.96	45.17±4.55	93.44±1.50	24.65±3.08	-2.3±1.49
P	13.25±0.88	7.28±0.02	89.22±8.45	50.41±5.12	91.21±1.32	23.55±2.39	-3.1±1.62
PD_{25}	12.42±1.72	7.29±0.03	89.05±9.36	48.71±5.71	91.62±2.33	22.65±2.67	-3.1±1.61
PD_{50}	13.15±1.83	7.28±0.02	91.82±7.41	50.91±6.32	91.42±1.85	23.11±3.45	-1.9±1.63
PD_{75}	13.24±1.51	7.28±0.03	87.24±10.23	46.57±5.31	90.62±3.15	23.34±3.10	-3.3±1.16
LYPD	12.41±1.33	7.30±0.02	88.62±7.82	49.48±4.49	91.02±2.25	22.85±2.74	-1.5±1.51
TDPD	13.10±1.51	7.29±0.03	89.02±7.50	48.88±2.89	90.82±2.19	22.85±2.77	-1.8±1.31

TABLE 2: EXPRESSION LEVELS OF PI3K mRNA, AKT mRNA, GSK-3β mRNA RELATIVE QUANTITY

Group	PI3K mRNA	Akt mRNA	GSK-3β mRNA
N	0.52±0.09	1.83±0.09	1.36±0.17
F	0.42±0.03	1.90±0.14	1.42±0.18
D	0.42±0.04	1.82±0.19	1.46±0.26

P	0.51±0.08	1.91±0.23	1.63±0.18①
PD_{25}	0.48±0.04	1.85±0.22	1.40±0.18
PD_{50}	0.47±0.11	1.77±0.36	1.38±0.18
PD_{75}	0.47±0.10	2.04±0.31	1.26±0.09②
LYPD	0.41±0.07①②	1.54±0.22①②	1.46±0.28
TDPD	0.45±0.03	1.92±0.20	1.080±0.18①②

Note: Compared with group N, ①$p<0.05$; compared with group P, ②$p<0.05$ and compared with the PD_{75} group, ③$p<0.05$

Western blot results showed that the expression levels of pAkt (ser473) and pGSK-3β (ser9) proteins in the P, PD_{25}, PD_{50}, PD_{75} and LYPD groups were significantly lower than those in the N group ($p<0.05$). There were no significant differences in the expression levels of Akt protein and GSK-3β protein between the PD_{25}, PD_{50}, PD_{75}, LYPD and TDPD groups compared to the P group ($p>0.05$), while the expression levels of pAkt (ser473) protein in the PD_{75} and TDPD groups, as well as pGSK-3β (ser9) protein in the PD_{25}, PD_{50}, PD_{75} and TDPD groups, were significantly higher than those in the P group ($p<0.05$). Moreover, the expression levels of pAkt (ser473) protein and pGSK-3β (ser9) protein in the LYPD group were significantly lower than those in the PD_{75} group ($p<0.05$), while the expression level of pGSK-3β (ser9) protein in the TDPD group was significantly higher than that in the PD_{75} group ($p<0.05$) as shown in Table 3.

The ratios of pAkt (ser473)/Akt and pGSK-3β (ser9)/GSK-3β in the F group, D group, PD_{75} group, and TDPD group were not significantly different from those in the N group ($p>0.05$). However, the ratios of pAkt (ser473)/Akt and pGSK-3β (ser9)/GSK-3β in the P, PD_{25}, PD_{50}, LYPD, and TDPD groups were significantly lower than those in the N group ($p<0.05$). Additionally, the ratios of pAkt (ser473)/Akt and pGSK-3β (ser9)/GSK-3β in the PD_{75} and TDPD groups were significantly higher than those in the P group ($p<0.05$). The ratios of pAkt (ser473)/Akt and pGSK-3β (ser9)/GSK-3β in the LYPD group were significantly lower than those in the PD_{75} group ($p<0.05$), while the ratios of pAkt (ser473)/Akt and pGSK-3β (ser9)/GSK-3β in the TDPD group were significantly higher than those in the PD_{75} group ($p<0.05$) as shown in Table 4.

N, F and D groups including the nuclei were large and round, with uniform chromatin density. Nucleoli were prominent and centrally located. Mitochondria exhibited normal morphology, and synaptic structures appeared normal.

In P group, the chromatin showed marginal aggregation, nuclear condensation and invaginations of the nuclear membrane. Mitochondria exhibited vacuolar degeneration and cristae fractures. There was a significant reduction in synaptic vesicles and postsynaptic dense bodies.

In PD_{25} group, similar to the P group, there were chromatin marginal aggregations and reduced synaptic vesicles and postsynaptic dense bodies. The synaptic cleft was unclear, and mitochondrial vacuolar degeneration was observed.

In PD_{50} group, the chromatin was reduced and partially condensed. Mitochondria showed mild vacuolar degeneration, and cristae were decreased and irregular. There was a reduction in synaptic vesicles and postsynaptic dense bodies.

In PD_{75} group, the chromatin was slightly reduced, with relatively uniform density. Mitochondria exhibited mild swelling and the synaptic cleft remained clear. There was a slight decrease in synaptic vesicles and postsynaptic dense bodies.

In LYPD group, the chromatin exhibited condensed marginal aggregations, nuclear condensation and partial nuclear membrane dissolution. Mitochondria showed vacuolar degeneration and cristae fractures. There was a significant reduction in synaptic vesicles and postsynaptic dense bodies.

In TDPD group, the nuclear morphology was largely normal, and mitochondria did not show swelling. Synaptic vesicles and postsynaptic dense bodies were mostly normal, and the synaptic cleft appeared clear.

Numerous studies have indicated that receiving general anesthesia during the neonatal or infant period may lead to sustained impairment of learning and memory functions, suggesting that the immature nervous system during the developmental stage might be susceptible to the effects of general anesthetics. Propofol is a commonly used intravenous anesthetic in clinical practice, primarily inducing

neurodegeneration in the developing brain neurons through the regulation of intracellular protein activity and signaling pathways, including apoptosis[7,8]. Dexmedetomidine, as a derivative of imidazole, acts as α-2 adrenoceptor agonist, producing sedative, analgesic, anxiolytic and sympatholytic effects, and it also exhibits neuroprotective effects against brain injury[9]. Recent studies have shown that dexmedetomidine can attenuate propofol-induced neuronal damage in the hippocampus of developing rats, but the mechanism by which dexmedetomidine exerts its protective effects through the PI3K/Akt/GSK-3β signaling pathway remains unclear. In this study, by establishing an experimental model, we found that propofol caused hippocampal neuronal damage in developing rats, and dexmedetomidine reversed the neurotoxicity of propofol, with LYPD group weakening the protective effect of dexmedetomidine on hippocampal neurons, while TDPD group enhancing the protective effect of dexmedetomidine on hippocampal neurons. These findings suggest that dexmedetomidine may reverse the neurotoxic effects of propofol through activation of the PI3K/Akt/GSK-3β signaling pathway.

The hippocampus plays a crucial role in converting short-term memory into long-term memory, as it is a critical brain region with abundant synaptic connections. Propofol, as an alkyl phenol derivative, acts on synapses after intravenous injection, regulating the release of presynaptic neurotransmitters and the function of postsynaptic receptors to produce anesthetic effects. Due to its strong lipophilicity, propofol quickly distributes from the bloodstream to various organs and tissues throughout the body. Additionally, Yuan *et al*.[10] found that high-dose propofol can terminate status epilepticus in many patients without significant side effects. However, experiments by Didem *et al*.[11] revealed that prolonged application of high-dose propofol for the treatment of persistent seizure resulted in increased mortality and impaired long-term memory in patients. In this study, we found that 100 mg/kg propofol caused ultrastructural damage to hippocampal neurons, manifested as chromatin marginal aggregation, nuclear condensation and mitochondrial vacuolar degeneration. Propofol did not significantly affect the expression of total Akt protein, Akt mRNA, GSK-3β protein, and GSK-3β mRNA in the hippocampus but significantly reduced the ratio of pAkt (ser473)/Akt and pGSK-3β (ser9)/GSK-3β. This suggests that propofol mainly damages developing rat hippocampal neurons by affecting protein activity. The main mechanism of general anesthetics involves either activating Gamma-Aminobutyric Acid (GABA) receptors or inhibiting N-Methyl-D-Aspartate (NMDA) receptors in the central nervous system to produce anesthetic effects. Although excessive stimulation of GABA receptors can enhance the excitability of immature neurons, it may also induce cell apoptosis and neurodegeneration.

TABLE 3: THE RELATIVE EXPRESSION LEVEL OF AKT, GSK-3β, PAKT (SER473), PGSK-3β (SER9) PROTEIN BY WESTERN BLOT

Group	Akt	p-Akt (ser473)	GSK-3β	pGSK-3β (ser9)
N	1.01±0.12	0.36±0.04	1.85±0.40	0.96±0.08
F	1.14±0.22	0.34±0.06	1.90±0.22	0.88±0.08
D	1.13±0.16	0.37±0.10	1.87±0.46	0.86±0.09
P	1.22±0.12	0.10±0.06①	1.58±0.18	0.26±0.16①
PD_{25}	1.31±0.24①	0.11±0.04①	1.97±0.31	0.75±0.16①②
PD_{50}	0.26±0.21	0.11±0.02①	2.01±0.45	0.78±0.13①②
PD_{75}	1.27±0.24	0.22±0.06①②	1.80±0.19	0.77±0.19①②
LYPD	1.33±0.28①	0.17±0.03①③	1.94±0.28	0.41±0.06①③
TDPD	1.24±0.19	0.30±0.08②	1.95±0.33	1.06±0.09②③

Note: Compared with group N, ①$p<0.05$; compared with group P, ②$p<0.05$ and compared with the PD_{75} group, ③$p<0.05$

TABLE 4: PAKT (SER473)/AKT AND PGSK-3β (SER9)/GSK-3β PROTEIN EXPRESSION RATIO

Group	pAkt (ser473)/Akt	pGSK-3β (ser9)/GSK-3β
N	0.37±0.02	0.55±0.06
F	0.33±0.03	0.50±0.07
D	0.34±0.04	0.51±0.11
P	0.07±0.03①	0.10±0.02①
$_{PD25}$	0.08±0.02①	0.31±0.10①②
PD_{50}	0.09±0.02①	0.35±0.05①②
PD_{75}	0.20±0.05①②	0.44±0.09②
LYPD	0.12±0.01①③	0.23±0.06①②③
TDPD	0.29±0.07①②③	0.57±0.12②③

Note: Compared with group N, ①p<0.05; compared with group P, ②p<0.05 and compared with the PD_{75} group, ③p<0.05

Dexmedetomidine is an effective α2-adrenergic receptor agonist with a half-life of about 6 min. As a novel anesthetic adjunct, it has sedative, analgesic, anxiolytic effects, and effectively inhibits sympathetic excitability and stress responses[12]. Animal experiments have shown that intravenous injections of 10-300 mg/kg dexmedetomidine selectively target α2-adrenergic receptors, while a 1000 mg/kg dose affects both α1 and α2-adrenergic receptors. Soliman *et al*.[13] found that dexmedetomidine improved the stability of hemodynamics during surgery and reduced the incidence of local myocardial ischemia. Furthermore, Li *et al*.[14] found that dexmedetomidine could promote the survival of hippocampal and cortical neurons *in vitro*, exhibiting neuroprotective effects. In this study, the RT-PCR and Western blot results showed that the expression of pAkt (ser473) in the PD_{75} group was significantly increased compared to the P group, and hippocampal neuronal damage in the PD_{75} group was significantly alleviated. In the LYPD group, the expression of pAkt (ser475) decreased, and hippocampal neuronal structural damage was significant[15]. In the TDPD group, the expression of pGSK-3β (ser9) increased, and the structure of hippocampal neurons was mostly normal. These findings suggest that dexmedetomidine may reduce propofol-induced neurotoxicity through the activation of the PI3K/Akt/GSK-3β signaling pathway[16].

In summary, propofol can cause damage to hippocampal neurons in developing rats. Dexmedetomidine can alleviate the damage caused by propofol to hippocampal neurons, and this protective effect may be related to the activation of the PI3K/Akt/GSK-3β signaling pathway.

Conflict of interests:

The authors declared no conflict of interests.

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