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Original Article

Dexmedetomidine pretreatment alleviates cerebral ischemia-reperfusion injury in rats through resisting oxidative damage and regulating TGF-β1/Smad2/3 signaling pathway

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Abstract: *Background:* Cerebral ischemia-reperfusion (I/R) injury is a clinical frequently-occurring and common disease. Dexmedetomidine (DEX), a novel highly selective α2A-adrenergic receptor agonist, has been widely used in various fields of clinic. The oxidative damage and transforming growth factor-β1 (TGF-β1)/Smad2/3 signaling pathway are involved in I/R injury. This study aimed to investigate the protective effects of DEX on cerebral I/R injury in rats through resisting oxidative stress and regulating TGF-β1/Smad2/3 signaling pathway. *Methods:* Fifty SD rats were randomly divided into sham-operation, I/R, and low-, middle- and high-dose DEX group, 10 rats in each group. In later four groups, the cerebral I/R model was established. In addition, at 30 min before establishment of I/R model, the low-, middle- and high-dose DEX group were intraperitoneally injected with DEX with dose of 10, 20 and 40 mg/kg, respectively. After 24 h from ischemia, the neurological deficit scores, serum tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-β) levels, brain water content (BWC), percentage of brain infarction area (BIA), brain tissue superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, malondialdehyde (MDA), cyclooxygenase (COX-2) and 5 lipoxygenase (5-LOX) level and TGF-β1 and phosphorylated Smad2/3 (p-Smad2/3) protein expression were determined. *Results:* After treatment, compared with I/R group, the neurological deficit score, BWC, percentages of BIA, serum TNF-α and IL-1β level, and brain tissue MDA, COX-2 and 5-LOX level in high-dose DEX group were significantly decreased, respectively ($P < 0.05$), and the brain tissue SOD and GSH-Px activity and TGF-β1 and p-Smad2/3 expression level in high-dose DEX group were significantly increased, respectively ($P < 0.05$). Pearson correlation analysis showed that, the brain tissue SOD and GSH-Px activity were positively correlated with brain tissue TGF-β1 and p-Smad2/3 level, respectively ($P < 0.05$ or $P < 0.01$) *Conclusion:* DEX pretreatment can alleviate the cerebral I/R injury in rats. The mechanism may be related to its resistance of oxidative damage and up-regulation of TGF-β1/Smad2/3 signaling pathway in brain tissue.

Keywords: Dexmedetomidine, ischemia/reperfusion, rats, oxidative stress, TGF-β1, Smad2/3

Introduction

Cerebrovascular diseases are the main diseases affecting human health and causing death and disability, among which the ischemic cerebrovascular disease is the most common. In the high-risk surgery in nervous system, heart and large vessels, elderly and critical illness, the risk of cerebral ischemia in perioperative period is very high [1]. The timely reperfusion in ischemic brain tissues is an effective measure for treating cerebral ischemia. It can make the ischemic brain tissues to obtain oxygen again for providing nutrients necessary for normal metabolism of brain and removing metabolic wastes [2]. However, the recent studies have found that, the further tissue damage or dysfunction often occur after the blood flow is restored in brain tissues. This is called cerebral ischemia-reperfusion (I/R) injury. In clinic, a variety of treatment modalities can alleviate this disease, but most of the patients suffer from disability or even death due to the lack of effective treatment [3].

Dexmedetomidine (DEX) is a novel highly selective α2A-adrenergic receptor agonist. DEX has the analgesic, sedative and anxiolytic effects.

In addition, it has functions in resisting sympathy, inhibiting stress response, stabilizing hemodynamics and reducing the dosage of anesthetics [4]. DEX has been widely used in various fields of clinic. Recent studies have found that DEX has brain protective effects. The possible mechanisms include its decreasing the catecholamine level, reducing the release of excitatory neurotransmitters and regulating the pathway of cell apoptosis [5, 6]. However, the exact protective mechanisms remain unclear, and the optimal dosage, time and manner of clinical medication are not clear.

At present, the researches on the mechanism of cerebral I/R injury are mainly focused on the aspects including excitatory neurotoxicity, oxidative damage, inflammatory response, etc. [7]. In addition, it is found that, the exogenous transforming growth factor-β1 (TGF-β1) can reduce the cerebral infarction volume and degeneration of neural cells after cerebral ischemia in rats. Newborn mice lacking TGF-β1 gene expression may exhibit extensive neuronal degeneration and significantly shorten survival time [8]. Therefore, TGF-β1 has the neuroprotective effects. Smad2/3 is the receptor of TGF-β1 pathway [9]. In cerebral I/R injury, TGF-β1 can prevent the oxidation damage and cell apoptosis through phosphorylation of downstream factor Smad2/3. Therefore, we hypothesize that, the brain protective effects of DEX are related to its action on oxidative damage and TGF-β1 pathway.

In this study, the protective effects of DEX on cerebral I/R injury in rats were investigated, and the mechanisms based on resistance of oxidative damage and regulation of TGF-β1 pathway were explored. The objective was to provide a basis for further clarifying the mechanism of DEX in prevention and treatment of I/R injury.

Materials and methods

Animal grouping and treatment

Fifty SD rats (260±30 g) were randomly divided into 5 groups: sham-operation group, I/R group, and low-, middle- and high-dose DEX group, 10 rats in each group. The sham operation group only underwent surgical exposure of the external carotid artery without causing ischemia. In model group, and low-, middle- and high-dose DEX group, the cerebral I/R model was established. In addition, at 30 min before establishment of I/R model, the low-, middle- and high-dose DEX group were intraperitoneally injected with DEX with dose of 10, 20 and 40 mg/kg, respectively, and the sham operation and I/R group were intraperitoneally injected with 1 ml of sterile saline, respectively.

Establishment of cerebral I/R model

Rats were fasted for 12 h before surgery. Then the cerebral I/R model was established by middle cerebral artery occlusion [10]. After anesthesia by intraperitoneal injection of 10% chloral hydrate with dose of 0.35 g/kg, the right common carotid artery, external carotid artery and internal carotid artery were exposed. The right middle cerebral artery was embolized with nylon thread, with suture depth of 18-20 mm. After blocking for 2 h, the nylon thread was removed, and the middle carotid artery blood flow was restored, thus the cerebral I/R model was successfully established.

Neurological deficit scoring

After 24 h from ischemia, the neurological deficit scoring was performed according to the scoring standard established by Longa et al [8] as follows: 0 point: asymptomatic; 1 point: the rats could not fully extend the forepaw or the Horner's syndrome appeared; 2 points: the rats turned around to the opposite side; 3 points: the rats dumped to the opposite side; 4 points: the rats could not walk spontaneously, with loss of consciousness.

Determination of serum tumor necrosis factor-α and interleukin-1β level

Three milliliter of blood was taken from the tight ventricle of rats. After centrifuging at 3000 r/min for 15 min, the supernatant was immediately obtained and was kept in 20°C refrigerator. The serum tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-β) level were determined using ELISA. The operations were according to the instructions of kits.

Determination of brain water content

Five rats were sacrificed by decapitation, and the left side of brain was immediately taken. After accurately weighing by electronic balance,

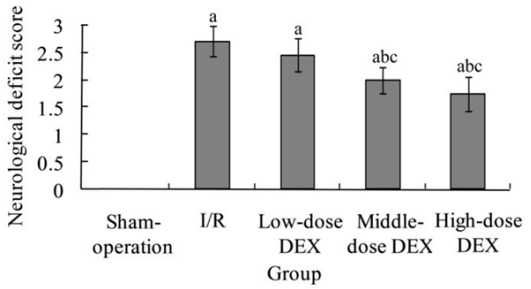

Figure 1. Neurological deficit scores of rats in different groups. [a]P < 0.01 compared with sham-operation group; [b]P < 0.05 compared with I/R group; [c]P < 0.05 compared with low-dose DEX group. I/R, ischemia-reperfusion; DEX, dexmedetomidine.

the brain tissue was placed in 110°C constant-temperature drying box for 24 h to constant weight (the difference of mass between two times of weighing was less than 0.2 mg). The dry brain tissue was accurately weighed using the same electronic balance. The brain water content (BWC) was calculated as follows: BWC (%) = [(Wet mass - Dry mass)/Wet mass] × 100.

Determination of percentage of brain infarction area

Brain tissue was taken from five rats, and was placed in the -20°C refrigerator for 20 min. Then the sections of brain tissue were prepared. From the optic chiasm, 1 slice of brain tissue was forward cut, and 4 slices of brain tissue were backward cut. The thickness of slice was 2 mm. These 5 slices were put into 1% TTC solution, strictly avoiding light, followed by incubation at 37°C for 30 min. The slices were turned over every 15 min. The slices were shifted to 10% formaldehyde for fixing for 3 h, followed by analyzing using BI-2000 medical image analysis system. The normal brain tissue after staining of presented red, and the infarction area presented white. The percentage of brain infarction area (BIA) was calculated [11].

Determination of oxidative stress indexes in brain tissue

Rat brain tissue was homogenized on the ice, followed by centrifuging at 4°C and 3500 r/min for 15 min. The supernatant was obtained. The superoxide dismutase (SOD) activity was determined using xanthine oxidase method. The glutathione peroxidase (GSH-Px) activity was determined using glutathione oxidation method. The malondialdehyde (MDA) level was determined using thiobarbituric acid method. The operations were according to the instructions of kits.

Determination of cyclooxygenase-2 and 5-lipoxygenase level in brain tissue

Supernatant of brain tissue was prepared. The protein content in the supernatant was detected by the biuret method. The cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) level in brain tissue of rats were determined using ELISA. The contents of COX-2 and 5-LOX in per gram of protein were calculated.

Determination of TGF-β1 and phosphorylated Smad2/3 protein expression in brain tissue

Expressions of TGF-β1 and phosphorylated Smad2/3 (p-Smad2/3) protein in brain tissue were determined by Western-blot method. The protein of brain tissue was extracted using RIPA lysis buffer (Sigma-Aldrich Corp., MO, USA) according to the manufacturer's instructions. The protein concentration was determined by Coomassie brilliant blue method. The protein concentration was adjusted to 50 μg/μL. The 10% SDS-PAGE (Sigma-Aldrich Corp., MO, USA) was performed for 4 h, then the separated protein was transferred to the PVDF membrane (Sigma-Aldrich Corp., MO, USA). After washing the membrane with PBS (Sigma-Aldrich Corp., MO, USA) for 2 times, 15 min for each time, l% BSA (Fuzhou Maixin Biotechnology Development Co., Ltd., Fuzhou, China) was used to block the non-specific antigen for 3 h. After blocking, the membranes were incubated with primary antibody overnight at 4°C, followed by washing with PBS. The horseradish peroxidase-labeled second antibody was added, followed by incubation at room temperature for 3 h. Visualization was accomplished by the enhanced chemiluminescence (ECL plus Western-blotting detection system, GE Healthcare Life Sciences, MA, USA). The intensity of bands was calculated using Image J analysis software (European Molecular Biology Laboratory Inc., Oxford, UK). The primary antibodies and secondary antibodies for TGF-β1 and p-Smad2/3 were provided by Shanghai Sangon Biological Engineering Technology and Service Co., Ltd. (Shanghai, China). β-actin (Sigma-Aldrich Corp., MO, USA) was used as the internal reference. The relative levels of TGF-β1 and p-Smad2/3 protein were

Table 1. BWC and percentage of BIA of rats in different groups

Group	BWC (%)	Percentage of BIA (%)
Sham-operation	77.91±1.22	0
I/R	80.75±1.45[a]	44.16±5.45[a]
Low-dose DEX	79.71±1.21[a]	39.92±4.27[a]
Middle-dose DEX	79.52±1.27[a]	22.45±3.72[a,b,c]
High-dose DEX	78.62±1.23[b]	21.21±3.45[a,b,c]

[a]P < 0.01 compared with sham-operation group; [b]P < 0.05 compared with I/R group; [c]P < 0.05 compared with low-dose DEX group. BWC, brain water content; BIA, brain infarction area; I/R, ischemia-reperfusion; DEX, dexmedetomidine.

Table 2. Serum TNF-α and IL-1β level of rats in different groups

Group	TNF-α (pg/ml)	IL-1β (pg/ml)
Sham-operation	118.56±10.34	17.71±2.01
I/R	166.61±12.11[a]	27.31±3.21[a]
Low-dose DEX	153.57±13.84[a,b]	26.27±1.37[a]
Middle-dose DEX	146.41±13.22[a,b]	22.39±3.04[a,b,c]
High-dose DEX	140.27±15.02[a,b]	20.52±3.28[a,b,c]

[a]P < 0.01 compared with sham-operation group; [b]P < 0.05 compared with I/R group; [c]P < 0.05 compared with low-dose DEX group. TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; I/R, ischemia-reperfusion; DEX, dexmedetomidine.

expressed as ratio of the optical density to β-actin for each sample.

Statistical analysis

All statistical analysis was carried out using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The data were presented as mean ± SD. The difference between two groups was analyzed using one-way analysis of variance with SNK-q test. The relationships between oxidative damage and TGF-β1/Smad2/3 signaling pathway were was investigated using Pearson correlation analysis. P < 0.05 was considered as statistically significant.

Results

Neurological deficit scores of rats

After 24 h from ischemia, compared with the sham-operation group, the neurological deficit scores of rats in I/R, low-, middle- and high-dose DEX group were significantly increased, respectively (P < 0.01). Compared with the I/R group, the neurological deficit scores in middle- and high-dose DEX group were significantly decreased, respectively (P < 0.05) (**Figure 1**).

BWC and percentage of BIA of rats

Compared with sham-operation group, the BWC in I/R group was significantly increased (P < 0.05). Compared with I/R group, the BWC in high-dose DEX group was significantly decreased (P < 0.05). In addition, compared with sham-operation group, the other four groups presented obvious brain infarction. Compared with I/R group, the percentages of BIA in middle- and high-dose DEX group were significantly decreased, respectively (P < 0.05) (**Table 1**).

Serum TNF-α and IL-1β level of rats

As shown in **Table 2**, the serum levels of TNF-α and IL-1β in I/R group were significantly higher than those in sham-operation group, respectively (P < 0.05). Compared with I/R group, the TNF-α level in low-, middle- and high-dose DEX group, and the IL-1β level in middle- and high-dose DEX group were significantly decreased, respectively (P < 0.05).

SOD and GSH-Px activity and MDA level in brain tissue of rats

Table 3 showed that, the SOD and GSH-Px activity in rat brain tissue of rats in I/R group were significantly lower than those in sham-operation, respectively (P < 0.05), and the MDA level in I/R group was significantly higher than that in sham-operation group (P < 0.05). Compared with I/R group, the SOD and GSH-Px activity in high-dose DEX group were significantly increased, respectively (P < 0.05), and the MDA level in high-dose DEX group was significantly decreased (P < 0.05).

COX-2 and 5-LOX level in brain tissue of rats

As shown in **Table 4**, the COX-2 and 5-LOX level in rat brain tissue in I/R group were significantly higher than those in sham-operation, respectively (P < 0.05). Compared with I/R group, the COX-2 level in middle- and high-dose DEX group was significantly decreased, respectively (P < 0.05), and 5-LOX level in high-dose DEX group was significantly decreased (P < 0.05).

TGF-β1 and p-Smad2/3 expression in brain tissue of rats

Table 5 showed that, the TGF-β1 and p-Smad2/3 expression level in brain tissue of rats in I/R, low-, middle- and high-dose DEX group were

Table 3. SOD and GSH-Px activity and MDA level in brain tissue of rats in different groups

Group	SOD (U/mg prot)	GSH-Px (U/mg prot)	MDA (nmol/mg prot)
Sham-operation	272.34±32.11	77.59±10.52	5.82±1.28
I/R	224.19±44.33[a]	51.13±11.37[a]	9.23±1.46[a]
Low-dose DEX	237.68±23.91[a]	59.34±8.34[a]	8.52±1.16[a]
Middle-dose DEX	249.34±35.72[c]	65.21±9.81[a]	8.22±0.98[a]
High-dose DEX	265.21±33.61[b,c]	74.47±10.28[b,c]	7.89±1.01[a,b]

[a]P < 0.01 compared with sham-operation group; [b]P < 0.05 compared with I/R group; [c]P < 0.05 compared with low-dose DEX group. SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; I/R, ischemia-reperfusion; DEX, dexmedetomidine.

Table 4. COX-2 and 5-LOX level in brain tissue of rats in different groups

Group	COX-2 (pg/g prot)	5-LOX (pg/g prot)
Sham-operation	23.23±2.83	2.84±0.32
I/R	32.06±4.45[a]	4.17±0.53[a]
Low-dose DEX	30.12±3.19[a]	4.02±0.56[a]
Middle-dose DEX	27.36±3.26[a,b]	3.74±0.41[a]
High-dose DEX	26.32±3.23[a,b,c]	3.34±0.42[a,b,c,d]

[a]P < 0.01 compared with sham-operation group; [b]P < 0.05 compared with I/R group; [c]P < 0.05 compared with low-dose DEX group; [d]P < 0.05 compared with middle-dose DEX group. COX-2, cyclooxygenase-2; 5-LOX, 5-lipoxygenase; I/R, ischemia-reperfusion; DEX, dexmedetomidine.

Table 5. TGF-β1 and p-Smad2/3 expression in brain tissue of rats in different groups

Group	TGF-β1/β-actin	p-Smad2/3/β-actin
Sham-operation	0.23±0.03	0.11±0.02
I/R	0.87±0.07[a]	0.72±0.06[a]
Low-dose DEX	0.97±0.08[a]	0.78±0.1[a]
Middle-dose DEX	1.12±0.13[a,b,c]	0.86±0.13[a]
High-dose DEX	1.34±0.11[a,b,c,d]	1.28±0.15[a,b,c,d]

[a]P < 0.01 compared with sham-operation group; [b]P < 0.05 compared with I/R group; [c]P < 0.05 compared with low-dose DEX group; [d]P < 0.05 compared with middle-dose DEX group. TGF-β1, transforming growth factor-β1; p-Smad2/3, phosphorylated Smad2/3; I/R, ischemia-reperfusion; DEX, dexmedetomidine.

significantly higher than those in sham-operation, respectively (P < 0.05). Compared with I/R group, the TGF-β1 level in middle- and high-dose DEX group was significantly increased, respectively (P < 0.05), and the p-Smad2/3 level in high-dose DEX group was significantly increased (P < 0.05).

Relationship between oxidative damage and TGF-β1/Smad2/3 signaling pathway

Pearson correlation analysis showed that, the brain tissue SOD and GSH-Px activity were positively correlated with brain tissue TGF-β1 and p-Smad2/3 level, respectively (SOD with TGF-β1: r = 0.821, P < 0.01; SOD with p-Smad2/3: r = 0.372, P < 0.05; GSH-Px with TGF-β1: r = 0.726, P < 0.01; GSH-Px with p-Smad2/3: r = 0.235, P < 0.05). The brain tissue MDA level was not significantly correlated with brain tissue TGF-β1 or p-Smad2/3 level (P > 0.05) (**Table 6**).

Discussion

Cerebrovascular diseases are the frequently-occurring and common diseases in clinic. In recent years, the incidence rate, mortality rate and disability rate of cerebrovascular diseases are increasing, which has become the main cause of disability and death in clinic. The ischemic cerebrovascular disease is the most common, especially the cerebral I/R injury [1]. Clarifying the mechanism related to cerebral I/R injury has been the focus of clinical and basic research. In this study, the cerebral I/R injury model of rats was established, and the protective effects of DEX pretreatment on cerebral I/R injury were investigated. Results showed that, after 24 h from ischemia, compared with the I/R group, the neurological deficit scores in middle- and high-dose DEX group were significantly decreased, the BWC in high-dose DEX group was significantly decreased, the percentages of BIA in middle- and high-dose DEX group were significantly decreased. This indicates that, the pretreatment using DEX with certain dose can mitigate the cerebral I/R injury in rats.

It is found that, the production of oxygen free radicals and their lipid peroxidation are one of the main mechanisms of I/R injury [12]. Under normal circumstances, the body can produce a small amount of free radicals, but they are quickly eliminated by free radical scavenging system in the body, and will not cause damage to the cells and tissue. In cerebral I/R ischemia, the function of free radical scavenging system declines. A large number of free radicals are

Table 6. Relationship between oxidative damage and TGF-β1/Smad2/3 signaling pathway

Index	SOD		GSH-Px		MDA	
	r	P	r	P	r	P
TGF-β1	0.821	< 0.01	0.726	< 0.01	-0.316	> 0.05
p-Smad2/3	0.372	< 0.05	0.235	< 0.05	-0.252	> 0.05

SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; TGF-β1, transforming growth factor-β1; p-Smad2/3, phosphorylated Smad2/3.

produced, which react with the polyunsaturated fatty acids in the phospholipid on biological membrane, thus producing large amounts of toxic lipid peroxides. The toxicity of MDA is the highest among the toxic lipid peroxides. The content of MDA can directly reflect the degree of lipid peroxidation, and indirectly reflect the degree of cell injury [13]. SOD is the most important antioxidant enzyme and free radical scavenger in the body. It can clear the oxygen free radical and terminate the chain reaction of free radicals, so as to protect the cell and tissue [14]. GSH-Px is a kind of important peroxide decomposition enzyme existing widely in the body. It can make the reduction of toxic peroxides into non-toxic hydroxyl compounds, thus protecting the structure and function of cell membrane from the damage of peroxides. The activity of GSH-Px can affect the antioxidant capacity of the body [15]. The results of this study showed that, the SOD and GSH-Px activity in rat brain tissue of rats in I/R group were significantly lower than those in sham-operation, and the MDA level in I/R group was significantly higher than that in sham-operation group. Compared with I/R group, the SOD and GSH-Px activity in rat brain tissue in high-dose DEX group were significantly increased, and the MDA level in high-dose DEX group was significantly decreased. This indicates that, the lipid peroxidation may be one of causes for cerebral I/R injury, and DEX pretreatment can resist the oxidative damage, thus exerting protective effects.

Inflammatory reaction plays an important role in the pathological process of cerebral ischemia. TNF-α is one of the major inflammatory cytokines, and has a wide range of biological characteristics. Under normal circumstances, TNF-α has the anti-infection, anti-tumor and tissue repair-promotion effects, which is beneficial to the body. Under the pathological state, TNF-α is persistently released, which will cause the tissue damage [16]. IL-1β is a strong inflammatory cell chemokine and immune-derived cytokine. IL-1β can cooperate with other cytokines to promote the activation of B cells and T cells [17]. In addition, IL-1β can induce the production of other inflammatory mediators and the expression of adhesion molecules, induce generation of free radicals and excitatory amino acids, and initiate the cascade reaction of cytokines, eventually leading to neuronal injury [18]. In the present study, compared with sham-operation group, the serum levels of TNF-α and IL-1β in I/R group were significantly increased. This is consistent with the result of previous researches. Compared with I/R group, the TNF-α level in low-, middle- and high-dose DEX group, and the IL-1β level in middle- and high-dose DEX group were significantly decreased. This indicates that, DEX pretreatment can decrease the TNF-α and IL-1β level in the body, which may be related to its protective effects.

Inflammation is a cascade response of inflammatory cells and inflammatory factors. It is a complex dynamic regulation process which involves the COX-2 and 5-LOX. COX-2 and 5-LOX are the key enzymes in the pathway in which the arachidonic acid is transformed into prostaglandins and leukotriene metabolites which play an important role in promoting inflammation, oxidation and the occurrence and growth of tumor [19]. A variety of factors including cytokinins, growth factors and tumor promoting factors can induce the expression of COX-2, which is involved in inflammation, proliferation and differentiation of cells [20]. 5-LOX and its metabolites can inhibit the cell apoptosis, and promote the angiogenesis [21]. Results of this study showed that, the COX-2 and 5-LOX level in rat brain tissue in I/R group were significantly higher than those in sham-operation. Compared with I/R group, the COX-2 level in middle- and high-dose DEX group was significantly decreased, and 5-LOX level in high-dose DEX group was significantly decreased. This indicates that, the elevation of COX-2 and 5-LOX level in brain may be involved in the mechanism of cerebral I/R injury in rats, and DEX pretreatment can lower the COX-2 and 5-LOX level, thus alleviate the injury.

TGF-β1 is a ubiquitous cytokine, and Smad2/3 is its receptor [9]. TGF-β1 is not expressed or weakly expressed in normal brain tissues. In

acute cerebral ischemic injury, TGF-β1 plays a role in anti-oxidation, preventing apoptosis, and modulating the inflammatory response through phosphorylation of downstream factor Smad2/3, thus regulating the microglia and astrocyte reaction. The increased expression of TGF-β in cerebral I/R injury may be due to the stress of nerve cells and glial cells induced by hypoxia and hypoxia [22]. TGF-β1 firstly activates the Smad2/3 pathway, and then activates inflammatory factors COX-2 and 5-LOX, thus regulates the inflammatory response [23, 24]. Results of this study showed that, the TGF-β1 and p-Smad2/3 expression level in brain tissue of rats in I/R were significantly higher than those in sham-operation. This is consistent with the result of previous researches. Compared with I/R group, the TGF-β1 level in middle- and high-dose DEX group was significantly increased, and the p-Smad2/3 level in high-dose DEX group was significantly increased. This indicates that, DEX pretreatment can further increase the expressions of TGF-β1 and p-Smad2/3 in brain tissue, thus exerting protective effects.

In conclusion, DEX preconditioning can alleviate the cerebral I/R injury in rats. The possible mechanism may be related to its resistance of oxidative damage and up-regulation of TGF-β1/Smad2/3 signaling pathway in brain tissue. This study has provided a basis for further clarifying the mechanism of DEX in prevention and treatment of cerebral I/R injury. However, the relationship of oxidative damage and TGF-β1/Smad2/3 signaling pathway in cerebral I/R injury and other mechanisms in protective effects of DEX on cerebral I/R injury need to be further studied.

Disclosure of conflict of interest

None.

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