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Mechanism of Dexmedetomidine Alleviating Myocardial Ischemia-Reperfusion Injury Through Mitochondrial and ER Oxidative Stress Pathway

Research Article

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Abstract

Objective: To analyze the mechanism of dexmedetomidine through mitochondrial and ER oxidative stress pathway in neonatal rat cardiomyocytes.

Methods: SD neonatal rats were selected as the research object, and the control group (Group A), H2O2 group (Group B), dexmedetomidine group (Group C) and dexmedetomidine + H2O2 group were constructed (Group D) four groups of neonatal rat cardiomyocyte oxidative injury models. After drug treatment, the morphology, LDH, GSH, ROS, casease-3,8,9 and 12 activities of neonatal rat cardiomyocytes were detected in turn. The mitochondrial membrane potential and apoptosis rate were detected by flow cytometry, and GRP78 and IRE1 were detected by Western blot α, Expression of Bcl-2 and Bax proteins.

Results: 500umol/l was selected as the best reaction concentration of H2O2. H2O2 can cause the disorder of cytoskeleton sequencing and the disappearance of myocardial striations, while dexmedetomidine can reduce the damage of H2O2 to cardiomyocytes. Compared with group A, the activity levels of LDH and ROS in cardiomyocytes in group B increased significantly, and the activity level of GSH decreased significantly. Compared with group B, the activity of GSH in group D was significantly increased, while the activity of LDH and ROS decreased significantly. Compared with group A, the activity levels of Caspase-3,8,9 and 12 in cardiomyocytes of group B increased significantly. Compared with group B, the activity of Caspase-3,8,9 and 12 in cardiomyocytes in group D decreased significantly. The apoptosis rate of cardiomyocytes in group A was (18.36 ± 5.68)%, and that in group D was (39.64 ± 9.36)%. Compared with group A, the apoptosis rate in group B increased significantly; there was no significant change in the apoptosis rate in group C. Compared with group A, the ratio of Bax to Bcl-2 in group B increased significantly; compared with group B, the ratio of Bax to Bcl-2 in group D decreased significantly. Compared with group A, GRP78 and IRE1 α Significantly improved; Compared with group B, GRP78 and IRE1 in group D α Significantly reduced.

Conclusion: Dexmedetomidine can inhibit the oxidative stress response and apoptosis induced by H2O2 in neonatal rat cardiomyocytes.

keywords: Dexmedetomidine; Mitochondria; Endoplasmic Reticulum; Oxidative Stress; Apoptosis; Myocardial Ischemia-Reperfusion

Introduction

Global cardiovascular diseases have become the biggest disease threatening human health. The incidence rate and mortality rate of coronary heart disease are the highest. The most commonly used treatment for patients with myocardial infarction is drug and surgical thrombolysis, However, ischemic myocardium is easy to cause Myocardial Ischemia-Reperfusion (IR) injury after reperfusion. At present, the effective myocardial protection measures are to complete ischemic preconditioning and post-treatment through physics and drugs. Oxidative stress Oxidative Stress (OS) refers to the functional damage and internal environment disorder caused by oxygen free radical production, calcium overload and inflammatory reaction when I/R injury occurs in myocardium. Generally, human reactive oxygen species will increase or the function of antioxidant defense system will decrease, which will also destroy the biological substances and functions of mitochondria and endoplasmic reticulum (ER) [1-3]. A large number of studies have shown that the main way of IR injury in cardiomyocytes is apoptosis, which is directly related to cell types, and mitochondria and ER are related to apoptosis. Dexmedetomidine

is a highly selective A2 adrenoceptor agonist. Its main function is inhibition. It is widely used in intensive care unit and surgery. Studies have confirmed that the drug can protect important organs under stress through A2 adrenoceptor [4-6]. Some scholars also pointed out that, Dexmedetomidine reduces myocardial I/R injury, which may be related to upstream mitochondrial adenosine triphosphate (adenosine triphosphate, ATP) sensitive potassium channel. At present, there is no formal report on the apoptosis signal pathway of mitochondrial and ER oxidative stress transformation in the medical field. In view of this, we studied the mechanism of dexmedetomidine on reducing cardiomyocyte I/R injury, in order to provide a scientific basis for the recovery of cardiomyocyte I/R injury.

Data and Research Methods

General Information

Experimental animals: 65 male Sprague Dawley (SD) rats, weighing 200 ± 10g, were used in the experiment. The source was Beijing weitonglihua company. The study was reviewed by the ethics committee of the PLA General Hospital.

Experimental equipment and reagents: The model of enzyme labeling instrument is TECAN and infinite 200 in Switzerland, and the fluorescence microscope is from Tokyo, Japan.

Fetal bovine serum is from GIBCO company of the United States, low sugar medium is from Luzhou Shengxin biological Co., Ltd., and type II collagenase is from sigma company of the United States. Lactate dehydrogenase from Nanjing Jiancheng Bioengineering Institute was used (Lactic Dehydrogenase; LDH), reduced Glutathione (GSH), reactive oxygen species (Reactive Oxygen Species; ROS) activity test kit; China's Bi Yun Tian company's pancreatic cell digestive juice, Western Blot gel preparation reagent, Casepase-3,8,9,12 activity detection kit; BD; BD membrane potential detection kit and apoptosis detection kit; China Boster company's mouse anti a-action; hermo of American hermo company Ot protein loading buffer and protein pre staining marker; H2O2 of sigma; Dexmedetomidine from Jiangsu Hengrui company, China; Donkey anti mouse fluorescent secondary antibody of British Abcam company; F-actin fluorescent probe of cytoskeleton company; Abcam Rabbit anti mouse GRP78 antibody; Rabbit anti mouse Bcl-2, Bax and ire1a primary antibodies from cell signaling company of the United States. The liquid required for the experiment is phosphate buffer solution and 5 × Running Buffer, 10 × Rotating membrane buffer, 5 × TBS, Western blot blocking solution, 10% separating gel, 5% concentrated gel.

Research Methods

Animal model preparation

The rats were anesthetized with 50mg/kg pentobarbital sodium, the suckling rats were fixed in the supine position, the heart was quickly removed and placed in the cold phosphate buffer solution, the excess parts such as fat were removed by ophthalmic scissors, transferred to the new phosphate buffer solution, the heart was cut into 1-3mm tissue blocks and the red blood cells were removed, placed in a sterile culture bottle and added with 0.125% trypsin cell digestive solution until immersion, After digesting at 4 for one day and removing the excess digestive solution, add fetal bovine serum to terminate trypsin digestion, then add type II collagenase digestive solution for multiple digestion, centrifuge, transfer the cell suspension to a 10cm Petri dish for culture for 2h, and remove most fibroblasts and endothelial cells through differential adhesion, Then, the medium containing 10% fetal bovine serum was diluted and inoculated into different culture plates and dishes, and then the inhibitory fibroblasts were added to ensure that the medium concentration was 10umol/L and cultured for 48h. Four groups of animal models were set up for research, There were 15 rats in each group: control group (group A), H2O2 group (group B), dexmedetomidine group (Group C) and dexmedetomidine + H2O2 group (Group D). Group A was added with normal medium, group B was added with H2O2 to ensure the concentration of 500umol/L, group C was added with dexmedetomidine to ensure the concentration of 5umol/L, and group D was added with dexmedetomidine to ensure the concentration of 5umol/L. after 2h, H2O2 was added to ensure the concentration of 500umol/L.

Cell immunofluorescence assay

FITC and F-actin were used to label a-actin and cytoskeleton to judge the morphological changes of cardiomyocytes. Cardiomyocytes were placed on glass slides, washed three times with phosphate buffer solution after 48 hours, fixed with 4% paraformaldehyde at room temperature for 20 minutes, perforated and sealed at 5% BSA room temperature for 1 hour, and then incubated with mouse anti-a-actin primary antibody at 4 overnight, The a-action labeled by FITC was incubated in the dark for 1H at room temperature, then incubated with F-actin fluorescent probe in the dark for 30min and labeled the cytoskeleton, and then passed through Diamidino Phenylindole Fluorescent Agent (DAPI) was incubated at room temperature in the dark for 10 min, and the nuclei were labeled, and finally detected under fluorescence microscope. The excitation wavelengths of DAPI, F-actin and a-action fluorescent probes were 405nm, 550nm and 488nm respectively.

LDH, GSH, ROS, casease-3, 8, 9, 12 activity detection

Determine the absorbance value from the microplate reader and obtain the LDH activity in the reaction system. Refer to the detection kit for the determination process. The absorbance value of the reaction product of GSH and 2-nitrobenzoic acid at 412nm is obtained by enzyme labeling instrument. Refer to the manual for the determination process. Sodium dihydrofluorescein diacetate was diluted with low glucose medium without fetal bovine serum The concentration of (DCFH-DA) was 10um. The cells were collected by flow cytometry. 1ml diluted DCFH-DA was added to each group of cells and incubated in the dark at 37 for 30min. After washing twice with phosphate buffer salt solution, it was resuspended with 600ul phosphate buffer salt solution, and finally tested by flow cytometry. The positive control reagent rosup in the positive control group was added 30min before the start of the test, and rosup after 30min It can significantly increase the level of ROS in cells. The activity of casease-3,8,9 and 12 can be measured by the absorbance value of PNA formed by catalysis of different substrates. The wavelength corresponding to the absorption peak is 405nm. The PNA of the control group was set to 1, and the other groups were standardized according to the control group.

Western blot detection

Firstly, cardiomyocytes were lysed, centrifuged and protein quantified to obtain total protein, 200ul cracking liquid is used (Radio Immunoprecipitation Assay; RIPA), the whole cracking operation was completed in ice, centrifugation was carried out at 14000r/min under the condition of 4 , and the total protein concentration was 1ug/UL after dilution by the cracking solution and loading buffer solution. After the determination was completed by BCA protein determination kit, it was boiled in a 100 dry bath for 10min and placed at - 20 for standby. Then, Western blot detection was carried out Including glue filling, sample loading, protein electrophoresis, membrane transfer, blocking, antibody incubation and development. Mix 5 at a volume ratio of 1:4 × The running buffer and samples are boiled at 99 for 15min and cooled. The sampling sequence is marker sample marker. The environment of electrophoresis experiment is bio rad vertical electrophoresis tank, the voltage of concentrated gel is 60V, and then 100V is used after the sample runs to the separation gel until all dyes reach the bottom of the gel. According to the distribution of the Marker strip and the molecular weight of the target protein, the gel layer is placed on the negative plate of the mould clamp according to the arrangement of the -3-layer filter paper sponge of the -3 filter paper-PVDF film. After the mold transfer, it is necessary to determine

whether to transfer the marker strip to the moving mold and make corresponding marks. Glucose regulatory protein 78 (Glucose regulated protein 78 GRP78), IRE1 α, The Rabbit anti mouse monoclonal antibodies against Bcl-2, Bax and GAPDH proteins were diluted in the ratio of 1:1000 through the diluent, and the incubation temperature was 4 . In the incubation stage of primary antibody and secondary antibody, special attention should be paid to the incubation time of secondary antibody should not be too long. The developer is DBA, and the image analysis is completed by Image Lab image analysis software.

Apoptosis and mitochondrial membrane potential

Apoptosis was detected by propionide iodide (Propidium Iodide, PI) and annexin V-FITC double labeling method. Annexin V can label apoptotic cells by binding phosphatidylserine. As a nucleic acid fuel, propyl iodide can dye the red nucleus. This detection method can identify the apoptotic period of cells. In the experiment, the mitochondrial membrane potential was detected by the fluorescence color generated by JC-1 fluorescent probe, and the existing form of JC-1 is related to that of mitochondria The function is related to the emitted fluorescence. The positive control group was added with oxidative phosphorylation uncoupling agent. When the mitochondrial membrane potential is high, JC-1 mostly exists in the mitochondrial matrix in the form of polymer and produces red fluorescence; When the mitochondrial membrane potential is low, most of JC-1 exists as monomers and the fluorescence color is green.

Statistical Methods

The data analysis software was spss23 0 statistical analysis software, the measurement data are expressed in the form of mean ± standard deviation, and the comparison between groups is analyzed by one-way variance. When $p < 0.05$, there was significant statistical difference between the two groups.

Results

Comparison of neonatal rat cardiomyocyte oxidative damage models under different H2O2 concentrations

The flow cytometry results of neonatal rat cardiomyocyte oxidative damage model under different H2O2 concentrations are shown in (Figure 1). The first quadrant, the second quadrant, the third quadrant and the fourth quadrant represent completely apoptotic cells, allowable error cells, normal living cells and early apoptotic cells respectively. Relevant literatures pointed out that the value range of H2O2 concentration in cell modeling was 100umol/l - 1mmol/L. the apoptosis rate of neonatal rat cardiomyocytes treated with different H2O2 concentrations for 6h was obtained by flow cytometry. The apoptosis rate refers to the sum of the first quadrant and the fourth quadrant. Overall, when the concentration of H2O2 was 500 umol/L, the apoptosis rate of neonatal rat cardiomyocyte oxidative injury model was about 50%. Therefore, 500umol/l was selected as the concentration of H2O2.

Morphological comparison of neonatal rat cardiomyocytes after drug treatment

The morphological comparison of cardiomyocytes of the four groups after drug treatment is shown in (Figure 2), showing the f-action labeled cytoskeleton, a-action labeled actin and DAPI stained nucleus. It can be seen that H2O2 will cause the disorder of cytoskeleton sequencing and the disappearance of myocardial striations. Dexmedetomidine will reduce the damage of H2O2 to cardiomyocytes and protect the cell structure.

Effects of dexmedetomidine on LDH, GSH and ROS in neonatal rat cardiomyocytes after H2O2 injury

The activity levels of LDH, GSH and ROS are the key indicators of oxidative stress response. The activity levels of LDH, GSH and ROS in neonatal rat cardiomyocytes after drug treatment were measured by ELISA and FCM. The specific results are shown in (Figure 3). (Figure 3 (a-c)) show the activity of LDH, GSH and ROS in neonatal rat cardiomyocytes respectively. Compared with the control group, the activity levels of LDH and ROS in cardiomyocytes increased significantly after 6h500umol/lh2o2 treatment, while the activity level of GSH decreased significantly ($P < 0.05$). Compared with H2O2 alone, the activity of GSH in cardiomyocytes increased significantly after the combined application of H2O2 + dexmedetomidine, while the activity of LDH and ROS decreased significantly ($P < 0.05$).

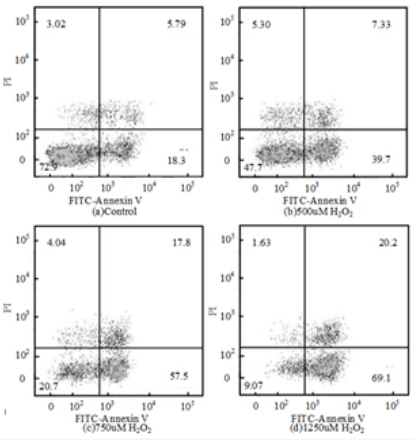

Figure 1: Flow cytometry results of neonatal rat cardiomyocyte oxidative damage model under different H2O2 concentrations.

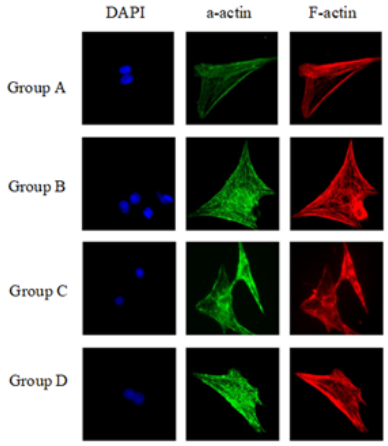

Figure 2: Morphological Comparison of cardiomyocytes in four groups after drug treatment ×600 times).

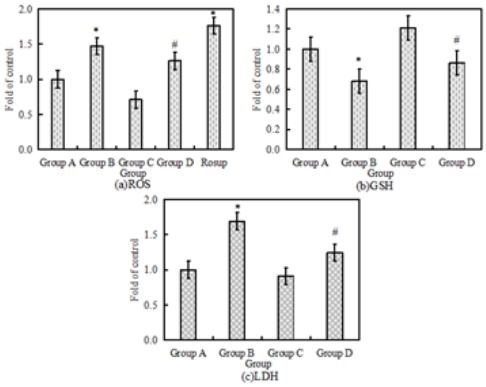

Figure 3: Effects of dexmedetomidine on LDH, GSH and ROS in neonatal rat cardiomyocytes.

Note: *indicates that the difference is statistically significant compared with group A# Compared with group B, the difference was statistically significant.

Effect of dexmedetomidine on caspase-3,8,9,12 activity in neonatal rat cardiomyocytes after H2O2 injury

The activity of intracellular apoptotic protease was detected by ELISA. The results are shown in Figure 4. Compared with the control group, the activity of Caspase-3,8,9 and 12 in cardiomyocytes was significantly improved after 6h500umol/lh2o2 treatment. After the combined application of H2O2 + dexmedetomidine, the activity of casease-3, 8, 9 and 12 in cardiomyocytes decreased significantly (P < 0.05).

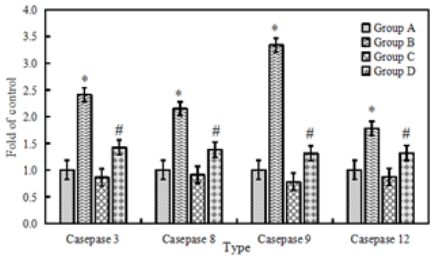

Figure 4: Effect of dexmedetomidine on Caspase-3, 8, 9 and 12 activity in neonatal rat cardiomyocytes.

Note: *indicates that the difference is statistically significant compared with group A# Compared with group B, the difference was statistically significant.

Effect of dexmedetomidine on cardiomyocyte apoptosis in neonatal rats after H2O2 injury

The effect of dexmedetomidine on cardiomyocyte apoptosis in neonatal rats was detected by flow cytometry. The results of flow cytometry are shown in (Figure 5). The apoptosis rate of the control group was (18.36 ± 5.68)%; After H2O2 treatment, the apoptosis rate increased, and the value was (57.69 ± 10.56)%; After H2O2 + dexmedetomidine combined application, the apoptosis rate decreased to a certain extent, and the value was (39.64 ± 9.36)%.

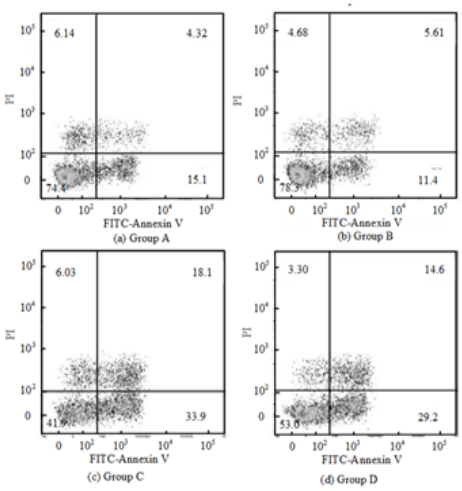

Figure 5: Effect of dexmedetomidine on cardiomyocyte apoptosis in neonatal rats.

Effect of dexmedetomidine on mitochondrial membrane potential of neonatal rat cardiomyocytes after H2O2 injury

Mitochondrial function can be reflected by mitochondrial membrane potential. The study was detected by flow cytometry. The results are shown in (Table 1). Compared with the control group, the mitochondrial membrane potential of cardiomyocytes decreased significantly after 6h500umol/lh2o2 treatment, and the difference was statistically significant (P < 0.05). After the combined application of H2O2 + dexmedetomidine, the mitochondrial membrane potential in cardiomyocytes further showed a significant downward trend, and the difference was statistically significant (P < 0.05).

Table 1: Effect of dexmedetomidine on mitochondrial membrane potential of neonatal rat cardiomyocytes JC-1 monomer/%).

	1h	2h	4h	6h
Group A	29	27	26	26
Group B	82*	75*	68*	61*
Group C	36	31	28	25
Group D	48#	42#	38#	34#
Positive control	89*	87*	86*	86*

Note: *indicates that the difference is statistically significant compared with group A# Compared with group B, the difference was statistically significant.

Effects of dexmedetomidine on GRP78 and IRE1 in neonatal rat cardiomyocytes after H2O2 injury α, Role of Bcl-2 and Bax

The ER stress response related proteins GRP78 and IRE1 were analyzed by Western blot α And anti apoptotic protein Bcl-2 and pro apoptotic protein Bax. Compared with the control group, the ratio of Bax to Bcl-2 in group B was significantly increased. However, after the combined application of H2O2 + dexmedetomidine, the ratio of Bax to Bcl-2 decreased significantly compared with group B. (Figure 6 (a,b))respectively show the results and data of Western blot detection of Bax and Bcl-2 in cardiomyocytes of four groups of neonatal rats. (Figure 7(a,b)) show GRP78 and IRE1 of neonatal rat cardiomyocytes in four groups respectively α, Western blot test results and data map of gpadh. Compared with the control group, GRP78 and IRE1 in group B α Significantly improved. Dexmedetomidine did not change GRP78 and IRE1 α But it can reduce the expression of GRP78 and IRE1 caused by H2O2 α Over expression.

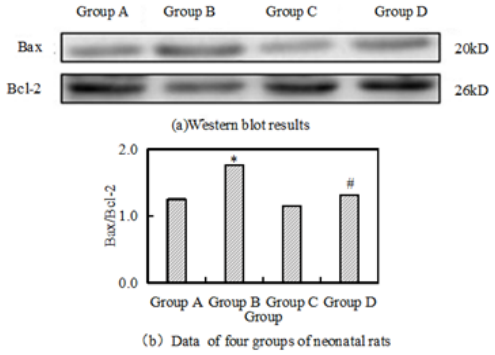

Figure 6: Western blot results and data of dexmedetomidine on Bax and Bcl-2 in neonatal rat cardiomyocytes.

Note: *indicates that the difference is statistically significant compared with group A# Compared with group B, the difference was statistically significant.

Discussion

Cardiovascular disease has become the highest mortality disease in China, which has an important impact on individuals and families. The oxidative stress model of neonatal rat cardiomyocytes was established by H2O2 to analyze the mechanism of dexmedetomidine

on neonatal rat cardiomyocytes with oxidative stress response [7-9]. At present, a large number of studies believe that dexmedetomidine can promote the balance of myocardial oxygen supply and demand, reduce myocardial oxygen consumption, reduce cardiac output and so on. Dexmedetomidine attenuates myocardial I/R injury by activating cell protection related signaling pathways. Relatively mature studies are mainly reflected in the following. Combined with A2 receptor and dexmedetomidine on cardiomyocytes, mek1-2-erk/2 and PI3K/Akt signaling pathways can improve myocardial capacity and ensure cell survival, so as to reduce infarct area. A large number of researchers believe that dexmedetomidine preconditioning can avoid myocardial ischemia-reperfusion injury by inhibiting signal pathway [10-12]. In vitro cell experiment, the concentration of dexmedetomidine was 0.01 nmol/l-600 umol/L, but no study confirmed the optimal action time and concentration of myocardial protection.

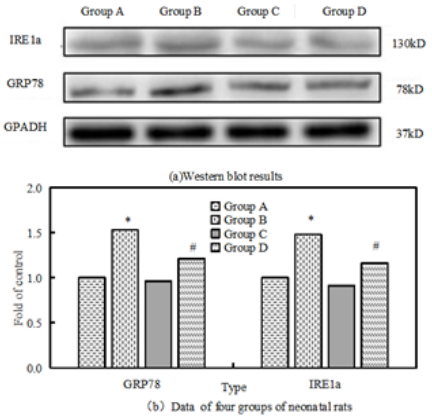

Figure 7: Four groups of neonatal rat cardiomyocytes GRP78 and IRE1 α, Western blot test results and data chart of gpadh.

Note: *indicates that the difference is statistically significant compared with group A# Compared with group B, the difference was statistically significant.

Dexmedetomidine protects cardiomyocytes through the apoptosis signal pathway transmitted by mitochondrial oxidative stress. Mitochondria will produce a large amount of ROS in the production stage. Under physiological conditions, ROS can repair tissues and protect the physiological function of cells. ROS overproduction will produce a very strong antioxidant capacity, which will promote the oxidative stress response of cardiomyocytes and eventually apoptosis. The main mechanism of myocardial I/R injury is cardiomyocyte apoptosis, and the most important pathway is mitochondrial apoptosis. Compared with group B, the activity of GSH in group D was significantly increased, while the activity of LDH and ROS decreased significantly. In group D, the activity of Caspase-3,8,9 and 12 in cardiomyocytes decreased significantly. Authoritative medical journals point out that the index of mitochondrial apoptosis pathway is the increase of caspase-3,8,9, expression and activity. Caspase-9 is the relatively upstream protease in the signal transduction stage of apoptosis. The protease can be activated not only by upstream caspase-8, but also by the complex of apafl and cytochrome c released by mitochondria. After caspase-9 is activated, Caspase-3, a key enzyme in the process of apoptosis signal transduction, can be activated to start the apoptosis program [13-15]. Some studies have also pointed out that caspase-3 is the downstream regulatory protein of Bcl-2 anti apoptotic protein. Living fossil protease can activate the enzymatic hydrolysis process of anti apoptotic protein. The cleavage product of this reaction exists in mitochondria. The cleavage product will promote cytochrome C in mitochondrial structure to enter the cytoplasm, and then cascade activate the family of apoptotic proteases to cause apoptosis [16-18]. Compared with group A, the mitochondrial membrane potential in group B decreased significantly. Compared with group A, the mitochondrial membrane potential in group B decreased significantly. Compared with group B, the ratio of Bax to Bcl-2 in group D decreased significantly.

A large number of scholars believe that apoptosis is closely related to endoplasmic reticulum stress. In the process of myocardial I/R, inflammatory reaction, calcium overload and oxidative stress can cause endoplasmic reticulum stress. GRP78 is the most important molecular chaperone in the endoplasmic reticulum. When the endoplasmic reticulum is stressed, GRP78 will alleviate the internal unfolded protein response [19-20]. Some studies have pointed out that GRP78 can bind to caspase-12 on the endoplasmic reticulum membrane after dissociation, and then inhibit the occurrence of apoptosis [21-22]. The markers of stress response in endoplasmic reticulum were GRP78 and IRE1 α Increased expression. The results showed that GRP78 and IRE1 in group D were significantly higher than those in group B α Significantly reduced. Compared with group B, the activity of caspase-12 in cardiomyocytes in group D decreased significantly.

Conclusion

Dexmedetomidine can alleviate the increase of casease-3,8,9,12 activity, ROS, LDH,GRP78 and IRE1 in neonatal rat cardiomyocytes caused by H2O2 α The expression increased, GSH activity decreased and mitochondrial membrane potential decreased. Dexmedetomidine can inhibit apoptosis through apoptosis signals transmitted by mitochondrial and ER oxidative stress, and then produce the function of protecting cardiomyocytes.

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