

ORIGINAL RESEARCH



Dexmedetomidine improves myocardial ischemia-reperfusion injury by increasing autophagy via PINK1/PRKN pathway

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Abstract

Ischemic heart disease poses a great threat to human life with its high morbidity and mortality. Timely reperfusion is considered as the most effective intervention for clinical treatment of myocardial ischemia. Reperfusion can commonly lead to cell death and myocardial injury. There has already been evidence that dexmedetomidine (DEX) can protect the injury of myocardial ischemia reperfusion (MI/R). The aims of this research are to explain DEX's functions in protecting MI/R injury as well as probing into its inner mechanisms. H9c2 cells was adopted to generate the injury of MI/R cell as a result of hypoxia/reoxygenation (H/R). MTT test was used to examine cell activity and flow cytometry was utilized to check cell apoptosis rate. Western blot test was adopted to appraise the protein expressions of Parkin RBR E3 ubiquitin protein ligase (PRKN or Parkin), PTEN-induced kinase-1 (PINK1) and markers associate with autophagy (Light Chain 3-II/I (LC3-II/I)). Immunofluorescence was applied to estimate the LC3 level. Next, the function of DEX in protecting the injury of H/R induced cell by PINK1/PRKN pathway was confirmed. DEX treatment significantly promoted viability, improved apoptotic rate and increased autophagy in H9c2 cells processed by H/R. Moreover, the protein expressions of PINK1 and PRKN were boosted by DEX, suggesting that DEX induced autophagy through the activation of PINK1/PRKN signaling pathway. In later tests, PINK1 teardown weakened DEX's effect the injury of myocardial cell induced by H/R. DEX improves MI/R injury by inducing autophagy through activating PINK1/PRKN pathway.

Keywords

Myocardial ischemia-reperfusion; Dexmedetomidine; Autophagy; Apoptosis; PINK1

1. Introduction

Ischemic heart disease poses lethal threat to human life with its lofty morbidity and mortality. Timely reperfusion is thought to be the most effective intervention for clinical treatment of myocardial ischemia, which can effectively inhibit myocardial cell apoptosis, reduce infarct area and restore cardiac dysfunction [1, 2]. However, reperfusion itself can also lead to cell death and myocardial injury, normally called injury of myocardial ischemia/reperfusion (MI/R) [2, 3]. MI/R triggers a complex inflammatory response that leads to more severe damage and arrhythmias, prevents recovery of systolic function and leads to cell death in ischemic tissue [4]. In recent years, accumulated studies demonstrated that autophagy possessed important role in MI/R injury [5]. Autophagy is an evolutionary conserved lysosomal dependent intracellular degradation pathway in eukaryotes that removes aging, damaged or denatured proteins and organelles to maintain homeostasis [6]. Previously published studies have shown that autophagy alleviates MI/R damage by providing sufficient

energy to myocardial cells and inhibiting cell apoptosis [7, 8]. Therefore, it is very important to find new drugs that closely related to the activity of autophagy activation that helps MI/R therapy.

As an α -2 adrenergic receptor agonist, dexmedetomidine (DEX) has the features of high selectivity and the function of calming, reducing anxiety, relieving pain and antihypertensive. It is clinically used as an adjunct to general anesthesia for short-term and long-term sedation in intensive care settings [9, 10]. The protective effect of DEX on ischemia/reperfusion (I/R)-related diseases has been extensively studied. A previous study showed that DEX inhibits MI/R injury by activating the Silent Information Regulator 1 (SIRT1)/mammalian target of rapamycin (mTOR) axis [11]. Recent studies have found that DEX could prevent cardiac dysfunction in septic rats by activating autophagy [12]. Yet, the mechanism of DEX's impact on leading to autophagy in MI/R requires more investigation.

PTEN-induced kinase-1 (PINK1) and Parkin RBR E3 ubiquitin protein ligase (PRKN) are autosomal recessive

Parkinson's disease (PD)-related genes which are connected to mitochondrial functions [13]. PINK1 of serine/threonine kinase exists in mitochondria, and PRKN is situated in cytoplasm. Commonly, PINK1 is treated and decomposed by mitochondrial proteases, when mitochondria are damaged or uncoupled, proteolysis of PINK1 is blocked. This results in the piling up of PINK1 in the outer membrane of mitochondria, where the cytoplasmic PRKN are next drawn by PINK1 for the ubiquitination of multiple mitochondrial outer membranes, thus removing damaged mitochondria by inducing autophagy [14, 15]. Recent studies have shown that DEX eliminated damaged mitochondria through PINK1-mediated mitochondrial autophagy, thereby alleviating lipopolysaccharide-induced macrophage apoptosis and inflammatory response [16]. In addition, Liu *et al.* [17] showed that enhancing PINK1-induced autophagy also significantly improved myocardial reperfusion injury.

According to these foundations, this study proposed a hypothesis that DEX may induce autophagy via activation of PINK1 and thus alleviate I/R damage. Therefore, in this study, DEX's cyto-protection in the injury of H/R will be probed into in H9c2 cells.

2. Materials and methods

2.1 Cell conditions

H9c2 cells, a Rat ventricular cardiomyocyte cell line, were bought from Otwo Biotech Inc (Shenzhen, China). Dulbecco's Modified Eagle Medium (DMEM) (Gibco/Invitrogen, USA) with 10% Foetal Bovine Serum (FBS) (Gibco) was used to develop the cells at 37 °C aided by 5% CO₂. Next, a three-gas thermostat containing 95% N₂, 5% CO₂ and 1% O₂ was used to incubate H9c2 cells for 4 h at 37 °C to establish hypoxia as described in a previous study [18]. Next, DEX at the concentrations of 0 μM, 0.5 μM, 1 μM and 1.5 μM was applied to stir the cells for 24 h. Then, the cells were gathered and prepared for the following assay.

2.2 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay

The liveliness of cells was checked by MTT assay [19]. First, 96-well plates planted with cells are set at 37 °C. Following that, 5 mg/mL MTT solution was poured in for the cell cultivation at 37 °C for 3 h. Then the liveliness of cells was evaluated by the absorbance shown at 450 nm with a microplate reader (Synergy H4 Hybrid, Biotek Instruments, USA).

2.3 Immunofluorescence

Cells were immobilized as long as thirty min with paraformaldehyde at the concentration of 4% and soaked with Triton X-100 at the concentration of 0.3% for 20 min. Following that, the cells and 10% phosphate buffer saline (PBS) were overlapped for 1 h and cultivated for a night with primary antibody. Next, they are incubated with secondary antibody for 1 h at normal room temperature during the next day. Next, DAPI was used to color the cells to show the nucleus. Eventually the cells were watched with a laser

scanning confocal microscope (Olympus IX51, Tokyo, Japan) [20].

2.4 Western blot assay

H9c2 cells' all protein was got with radioimmunoprecipitation (RIPA) lysate buffer. A BCA kit (Beyotime, Shanghai, China) was applied to assess the protein concentration. sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was utilized to isolate an equal amount of total protein. Then the protein was moved to the poly vinylidene difluoride (PVDF) membrane (Millipore Corp, USA), which was then interdicted with fat-free milk at the concentration of 5% for 1 h at normal room temperature and developed with the primary antibody at 4 °C for a night. The primary antibodies contains LC3 (#ab192890, Abcam, Cambridge, MA, USA; 1:1000), Bax (ab32503, Abcam; 1:1000), Bcl-2 (ab692, Abcam; 1:1000), PINK1 (ab186315, Abcam; 1:1000), glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (ab8245, Abcam; 1:1000), PRKN (179812, Abcam; 1:1000). Then, membranes were washed using Tris buffer salt solution with 1% Tween-20 (TTBS) for 3 times of 5 min each time. Next, incubating the membranes with second antibodies (Cell Signaling Technology (CST), Beverly, MA, USA; 1:2500) at room temperature for 1 h. An chemiluminescence system with enhanced function was used to watch the protein bands, which was quantified by means of Image-Pro Plus (Media Cybernetics, Silver Spring, USA) and GAPDH plays the internal control role.

2.5 Flow cytometry assay

Cell apoptosis was detected in accordance with the protocol of the Apoptosis Assay Kit (BD Biosciences, USA). The cells were made to float again after they are reaped, with propidium iodide and fluorescein isothiocyanate-Annexin V added. Following that, the treated cells were cultivated in darkness for 15 min [21]. Staining cells were then analyzed using FACS Calibur system (BD Biosciences, USA).

2.6 Cell transfection

Small interfering RNA against PINK1 (si-PINK1) and si-PINK1 negative control (si-NC) was obtained from shanghai Genepharma company (Shanghai, China). Seeding cells in 6-well plates with the density of 40–50% and then RiboFECTTM CP transfection Reagent (RiboBio Co, Guangzhou, China) was applied to make the cells affected with si-PINK1 or si-NC following the manufacturer's instructions.

2.7 Statistical analysis

GraphPad Prism (version 9.0.2, Graphpad Software, San Diego, CA, USA,) was utilized to analyze the data by one-way variance analysis (ANOVA). Data were reported as mean ± standard deviation (SD) of at least three independent tests, with $p < 0.05$ as significant differences.

3. Results

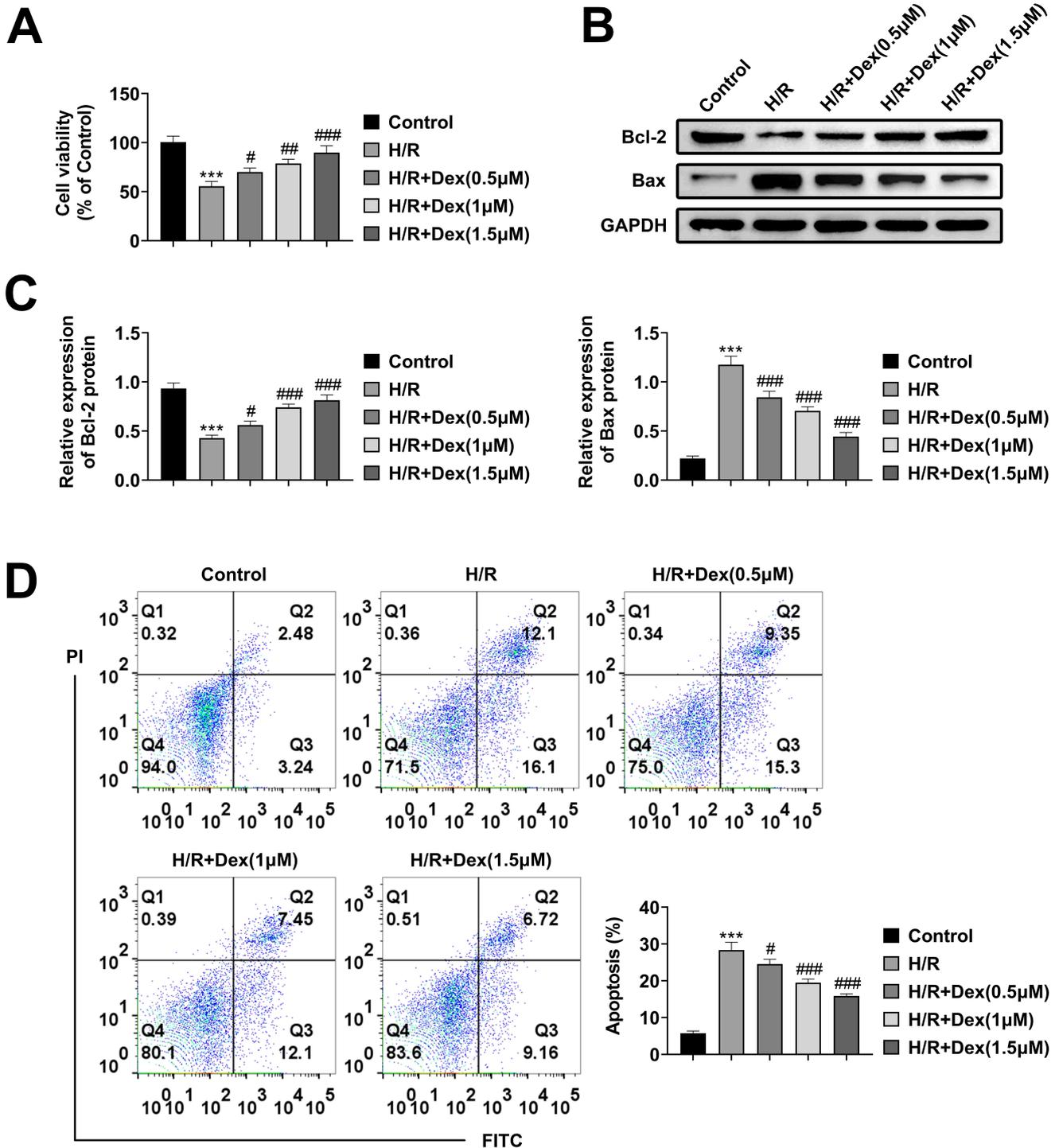


FIGURE 1. DEX protected against H/R induced injury in H9c2 cells. H/R was applied to trigger injury in H9c2 cells, and then were processed with DEX (0, 0.5, 1.0, 1.5 μM) for 24 h. (A) Cell liveliness was tested by MTT assay. (B) The protein amount of Bcl-2 and Bax. (C) The quantitative analysis of B. (D) Cell apoptosis were assessed by flow cytometry. The data was reported as mean ± SD. ****p* < 0.001, vs. the control group. #*p* < 0.05, ##*p* < 0.01 and ###*p* < 0.001, vs. H/R group.

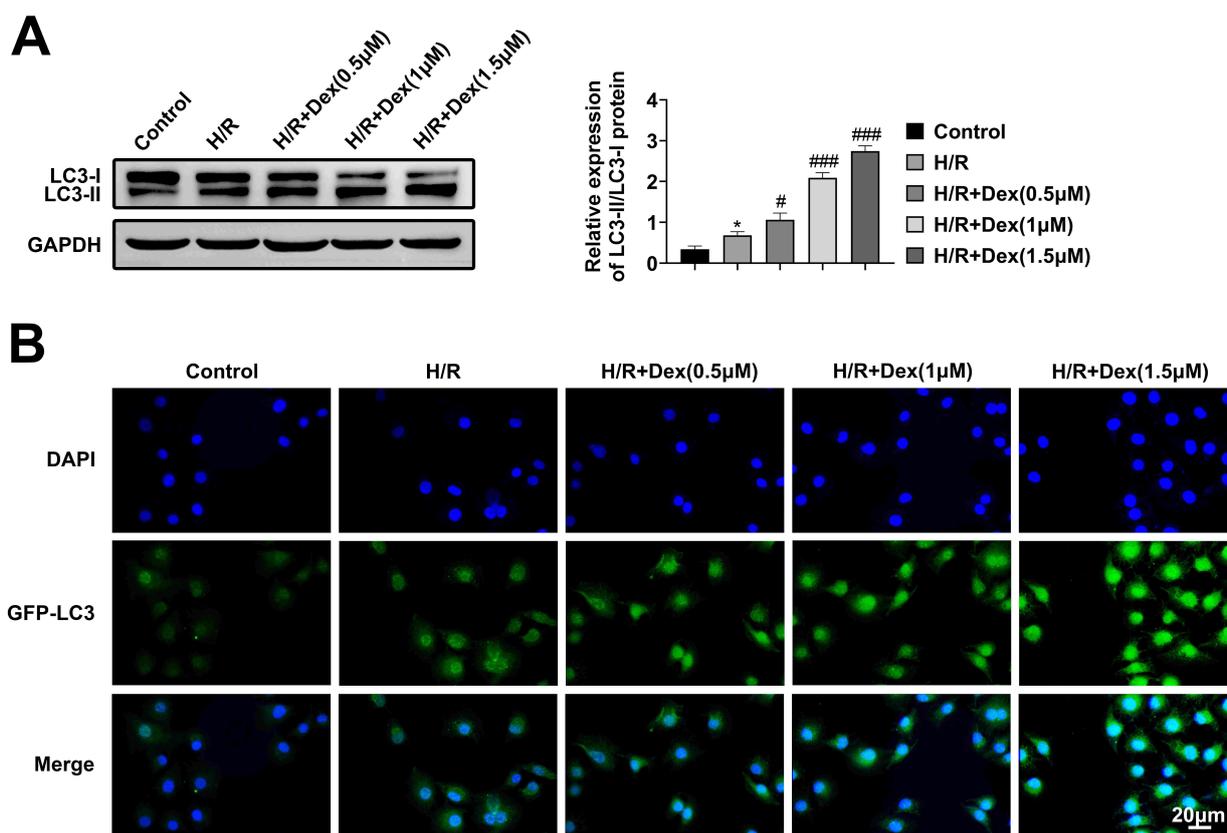


FIGURE 2. DEX worsened autophagy in H/R caused H9c2 cells. (A) LC3-II/LC3-I protein level was tested with western-blot assay. (B) LC3 expression level in each group was examined with immunofluorescence in H9c2 cells. Data was reported as mean \pm SD. * $p < 0.05$, vs. control group. # $p < 0.05$, ## $p < 0.01$ and ### $p < 0.001$, vs. H/R group.

3.1 DEX protected against H/R induced injury in H9c2 cells

The research found that the viability of H9c2 cells treated by H/R was significantly enhanced with DEX in comparison with that with no DEX process (Fig. 1A). To assess the impact of DEX on the apoptosis of H9c2 cells treated by H/R, flow cytometry test was used to evaluate the apoptotic cells, and Bax and Bcl-2 expressions were measured by western-blot test. Comparing with the control group, H/R treatment eminently enhanced the apoptosis of H9c2 cells treated by H/R. Nevertheless, the apoptotic rate obviously fell down after DEX process in a dose-dependent way (Fig. 1B–C). Bcl-2 is an anti-apoptotic protein, which inhibits mitochondrial permeability and cell death by interacting with Bax and Bak. Thus, enhanced Bcl-2 expression may increase cell resistance to apoptosis, as it does in tumor cells. The Bcl-2/Bax ratio functions like a “rheostat” which adjust cell mortality in line with the balance between Bcl-2 and Bax in cells [22]. The results of this research show Bax’s protein level was significantly increased, while that of Bcl-2 fell down in H/R-treated H9c2 cells, indicating high apoptotic rate. However, this phenomenon was reversed after DEX treatment in H9c2 cells. The same results were shown by flow cytometry assay (Fig. 1D). They suggested that DEX was able to enhance H9c2 cell survival and prevent H9c2 cells from injury induced by H/R.

3.2 DEX aggravated autophagy in H/R induced H9c2 cells

H/R reportedly induced cell injury by autophagy [5]. Therefore, to verify DEX’s impact on autophagy, western-blotting and immunofluorescence tests were carried out in H9c2 cells. As is illustrated in Fig. 2A, H/R process eminently increased the protein amount of LC3 in H9c2 cells comparatively. Nevertheless, DEX process further up-regulated adjusted LC3 protein level in a dose-dependent way, indicating its effect on aggravating autophagy activity. Immunofluorescence assay showed the consistent results (Fig. 2B).

3.3 DEX promoted the protein expressions of PINK1 and PRKN in H9c2 cells

PINK1 and PRKN act synergistically to sense mitochondrial functional status and label impaired mitochondria through autophagy in mammalian cells. Next PINK1’s and PRKN’s protein levels were measured in H9c2 cells treated with both H/R and DEX. Western-blot indicated that PINK1’s and PRKN’s protein levels were enhanced in H/R-treated cells (Fig. 3). Furthermore, DEX process further boosted the protein amount of PINK1 and PRKN, which had close relation with the improvement in autophagy activity.

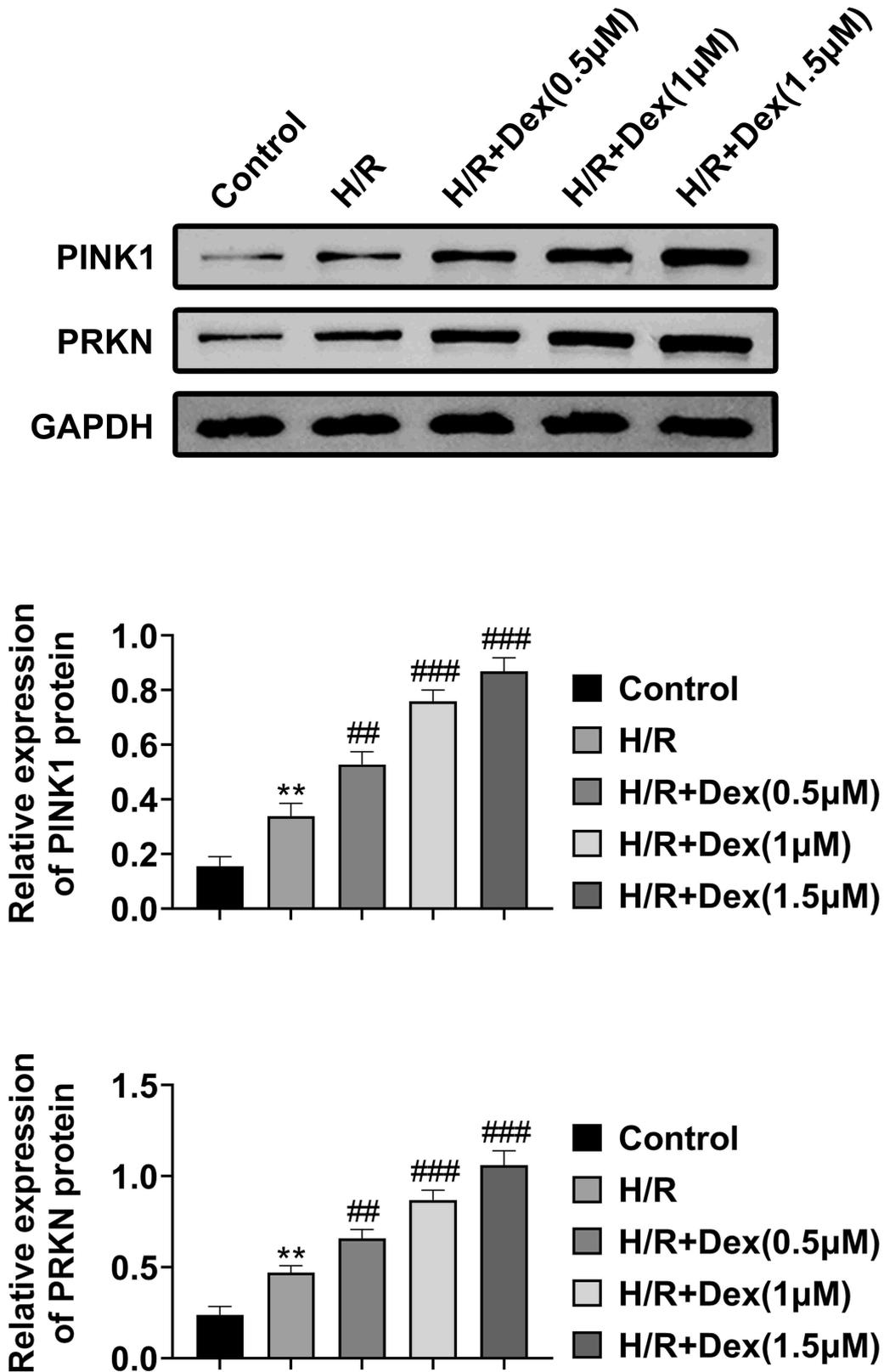


FIGURE 3. DEX increased PINK1 and PRKN expression in H9c2 cells. PINK1 and PRKN protein levels were assessed by western-blot test in H9c2 cells. Data were reported as mean \pm SD. ** $p < 0.01$, vs. control group. ## $p < 0.01$ and ### $p < 0.001$, vs. H/R group.

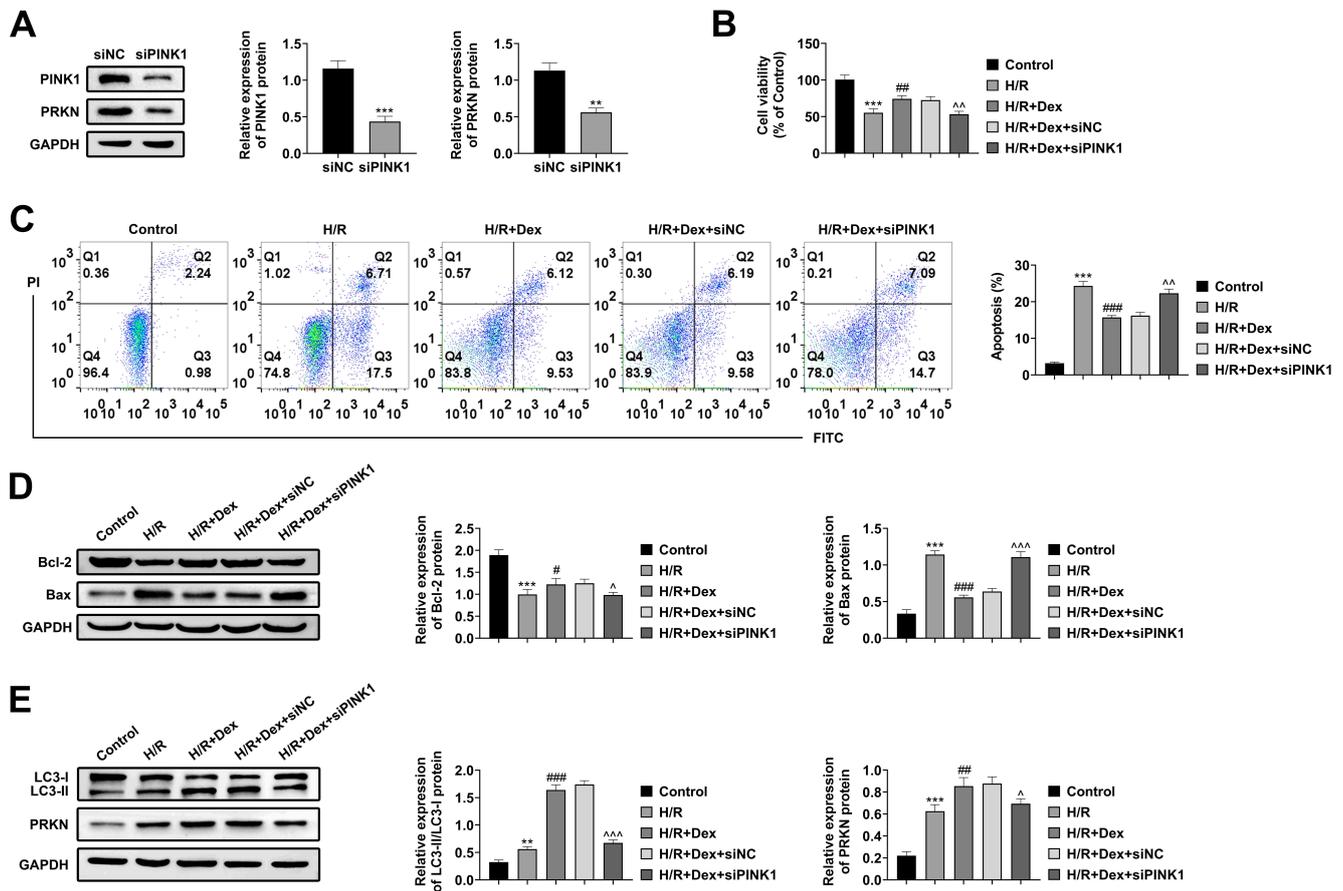


FIGURE 4. DEX lessened cell injury caused by boosting PINK1-mediated autophagy in H/R caused H9c2 cells. (A) PINK1 and PRKN proteins level in H9c2 cells transfected with si-NC or si-PINK1. (B) MTT assay for cell viability. (C) Cell apoptosis rate was examined by flow cytometry. (D) Western-blot tests showed protein level of Bcl-2 and Bax. (E) LC3-II/LC3-I proteins level in H9c2 cells. Data was reported as mean \pm SD. ** $p < 0.01$ and *** $p < 0.001$, vs. control group. # $p < 0.05$, ## $p < 0.01$ and ### $p < 0.001$, vs. H/R group. A $p < 0.05$, AA $p < 0.01$, and AAA $p < 0.001$, vs. H/R + DEX + si-PINK1 group.

3.4 DEX alleviated H/R induced H9c2 cell injury by promoting PINK1-mediated autophagy

It is believed that PINK1 accumulation induces mitochondrial autophagy and alleviates cell apoptosis. Therefore, to test PINK1's impact on H/R induced cell apoptosis, si-RNA was applied to interdict PINK1 expression. PINK1 protein level fell down in H9c2 cells transfected with si-PINK1, indicating its successful transfection into H9c2 cells. In addition, si-PINK1 resulted in the reduced protein level of PRKN, further indicating that PRKN function is dependent on PINK1 (Fig. 4A). MTT assay indicated that PINK1 knockdown removed DEX protection against H/R induced cell injury in viability (Fig. 4B) and lessened DEX impact on H/R induced apoptosis in H9c2 cells (Fig. 4C), proved by boosting Bax protein level and reduced Bcl-2 protein amount (Fig. 4D). Furthermore, autophagy was reduced as LC3-II/LC3-I's protein level was obviously decreased in H/R + DEX + si-PINK1 group compared with H/R + DEX group, suggesting that autophagy stirred by DEX in H9c2 cells treated by H/R was interdicted by PINK1 knockdown (Fig. 4E). Therefore, the results of the research indicate that DEX's protection on H/R

induced H9c2 cell injury is dependent on the existence of PINK1.

4. Discussion

This research shows the DEX's therapeutic impact on H/R induced H9c2 cell injury and its mechanism was revealed. DEX was shown to have enhanced cell viability, lessened cell apoptosis, and boosted autophagy in H/R-treated H9c2 cells. More experiments have revealed that DEX improved H9c2 cell injury induced by H/R via making PINK1/PRKN elevate cytoprotective autophagy (Fig. 3, 4).

MI/R is a pathological process of increasing weakening of tissue injury when ischemic myocardium recover to normally perfuse after partial or entire acute coronary artery occlusion, which serves as a vital element in the morbidity and mortality of coronary heart disease patients [23]. DEX is a safe and reliable new drug with strong sedative and analgesic ability. Increasing studies have proved that DEX has broad application prospects in the treatment of myocardial diseases in the future [24, 25]. Previous research has suggested that DEX reduced MI/R injury by lessening oxidative stress, cardiomyocyte apoptosis, and inflammatory reactions [11, 26, 27]. Nev-

ertheless, the mechanism at the molecular level of DEX's protection against MI/R injury requires more investigations.

Autophagy effect in heart tissue seems to be in double ways [28]. In the normal state, autophagy has a cellular protective effect and promotes normal cardiac function and has a positive effect on cell restore in the process of transient myocardial ischemia. But post-ischemia reperfusion is able to trigger autophagy overload, leading to cytotoxic effect, for example, extreme degradation and self-digestion of vital cellular parts, that is, autophagy or Class II programmed cell death [5, 29, 30]. Recently, an evidence has found that moderate up-regulation of autophagy can protect cardiomyocytes from I/R injury [31]. Similarly, this research revealed that DEX increases autophagy and eliminates H9c2 cell injury generated by H/R. Moreover, up-regulation of autophagy by Pink1/Parkin defends against MI/R. It is thus speculated that the enhanced cell activity regulated by DEX was related to autophagy and PINK1/PRKN pathway in H/R processed H9c2 cells. To verify it, the impact between DEX, autophagy and PINK1/PRKN was also tested. Western blot test revealed that DEX obviously enhanced the up-regulation of PINK1, PRKN and LC3-II/LC3-I ratio in H9c2 cells triggered by H/R. Moreover, immunofluorescence test suggested that DEX improved autophagy activity. To further confirm the role of PINK1/PRKN pathway in myocardial protection of DEX, H9c2 cells were pretreated with si-PINK1. As is anticipated, PINK1's and PRKN's protein levels were reduced by si-PINK1, and the effects of DEX1 on the enhancement in cell viability, inhibition of apoptosis and up-regulation of autophagy were all eliminated greatly. Therefore, these above data suggested that activation of PINK1/PRKN pathway to promote autophagy is a key protective mechanism of DEX against MI/R.

5. Conclusions

In conclusion, DEX enhances viability, lessens apoptosis rate and boost autophagy liveliness in H/R treated H9c2 cells. These *in vitro* experimental results indicated that DEX protects H/R induced cardiomyocyte injury via activation of PINK1/PRKN mediated autophagy, which provides a new perspective for the cardioprotective effect of DEX.

AUTHOR CONTRIBUTIONS

LL, XJ and XH—designed the study and carried them out, supervised the data collection, analyzed the data, interpreted the data, prepare the manuscript for publication, and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Lu Liu, Xiaojun Ji, Xumei Huang. Dexmedetomidine improves myocardial ischemia-reperfusion injury by increasing autophagy via PINK1/PRKN pathway. *Signa Vitae*. 2022; 18(5): 125-132. doi:10.22514/sv.2022.061.