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Original Article

Lidocaine Alleviates Myocardial Ischemia-Reperfusion Injury in Rats through JNK Signaling Pathway

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ABSTRACT

Aim/Background: This study aimed to explore the impact of lidocaine on rats subjected to MIR injury and to elucidate the underlying mechanisms involved in this process. The objective was to examine how lidocaine affects the physiological and biochemical responses in these rats, providing insights into its potential therapeutic benefits and the specific pathways through which it exerts its effects. **Materials and Methods:** 30 Sprague-Dawley rats were randomly divided into three groups: a sham group (*n*=10), a reperfusion group (*n*=10), and a lidocaine group (*n*=10). The MIR model was established in both the reperfusion and lidocaine groups. Following reperfusion, various cardiac function indexes were measured. Additionally, serum levels of LDH and CK were determined, and the infarct size was assessed using chemical colorimetry. To evaluate the expressions of JNK and NF-κB, WB and RT-PCR were performed. Changes in myocardial cell morphology, cardiac mesenchyme, and myofilaments were observed via HE staining. **Results:** Compared with reperfusion group, lidocaine group exhibited increased LVSP, FS and EF, decreased LVEDP, raised serum LDH and CK levels and reduced myocardial infarct size. According to the WB results, the expression of p-JNK protein declined, while that of NF-κB rose in lidocaine group in comparison with those in reperfusion group ($p<0.05$). **Conclusion:** Lidocaine can regulate the JNK signaling pathway to alleviate the MIR injury in rats.

Keywords: C-Jun N-terminal kinase, Myocardial ischemia-reperfusion, Lidocaine, Rats.

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INTRODUCTION

Myocardial Ischemia-Reperfusion (MIR) refers to the restoration of blood perfusion after the blood flow to the myocardium is blocked for a certain time, thus causing injury and dysfunction in the ischemia zone.[1] MIR can compromise cardiac function and harm myocardial cells, thereby elevating the risk of cardiovascular events such as myocardial infarction and arrhythmia. These complications can significantly deteriorate the prognosis of pre-existing medical conditions. By exacerbating heart problems and leading to more severe outcomes, MIR underscores the need for careful monitoring and management of patients with cardiovascular issues.[2,3] Therefore, it is of great significance to treat MIR for improving the therapeutic effect on cardiovascular diseases.

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MIR activates many intracellular signaling pathways.[4,5] In the realm of cellular biology, the MAPK family plays a crucial regulatory role, comprising ERKs such as ERK1/2, along with p42, p44, JNK, and p38. The first identified members of this family, ERK1/2, were discovered in 1990. Research indicates that the activation of ERKs promotes myocardial cell survival, thereby offering a protective compensation against antioxidant imbalance. In contrast, p38 MAPK and JNK are known to accelerate cellular apoptosis. Particularly noteworthy is the increased activation of JNK in MIRI. D-JNKI-1, a specific inhibitor of JNK, has been shown to enhance cardiac function while concurrently inhibiting Caspase-3 activation and apoptosis in isolated rat hearts.[6] Moreover, it decreases *in vivo* MIS. According to the observations of Kumar *et al.*,[7] the activity of p38 MAPK is increased about twice in the isolated hearts of the rats receiving MIR treatment. Besides, inhibiting p38 MAPK can decrease the MIS in the heart of the mice undergoing MIR. A recent study uncovered that the JNK pathway is associated with ischemia/reperfusion injury.[8]

Lidocaine is reported to be a widely applied local anesthetic and voltage-sensitive sodium channel blocker that can mitigate

cytokine-induced cellular injuries.[9] The use of lidocaine in the treatment of myocardial ischemia has demonstrated an ability to enhance various functional parameters, including cardiac contractility, in studies utilizing an implanted artificial Langendorff heart assay. Additionally, lidocaine has been shown to significantly improve static parameters, such as the histological infarct size, in *in vivo* models within a remarkably short period. This suggests its efficacy in both laboratory and living organism settings for myocardial ischemia management.[10] This study is designed to explore how lidocaine influences the expression levels of JNK within the context of MIR.

MATERIALS AND METHODS

Materials

A total of 30 SD rats weighing 220-240 g were fed in separate cages (60×51×35 cm, W×D×H) at (22±2)°C and (40±20)% humidity and given water and specific granular food. After adaptive feeding for 1 week, the rats were randomly grouped and weighed. This study was approved by the Animal Ethics Committee of Tianjin Medical University Animal Center.

Main reagents and instruments

Agarose and RIPA buffer were purchased from Yeasen Biotech Co., Ltd. (Shanghai, China), β-actin from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA), Hitachi 7600-020 automatic biochemistry analyzer from Hitachi Limited (Tokyo, Japan), FA2004A electronic scale Shanghai shunyu hengping scientific instrument Co. Ltd. (Shanghai, China), DK-8AD electrothermal constant-temperature water tank from Shanghai Yiheng Scientific Instrument Co. Ltd. (Shanghai, China), TL-4 benchtop centrifuge from Shanghai Bajiu Industrial Co. Ltd. (Shanghai, China), XHF-D in-line homogenizer from Ningbo, China, EON automatic microplate reader from the USA, RIPA lysis buffer, BCA protein assay kit and re-stained protein markers from Keygen (Nanjing, China), and citicoline from Shandong Qilu Pharmaceutical Group Co., Ltd. (Jinan, China).

Establishment of laboratory animal models

Thirty healthy male SD rats (220-240 g) were randomly divided into three groups: sham (n=10), reperfusion (n=10), and lidocaine (n=10). Coronary artery ligation was performed in the reperfusion and lidocaine groups. Anesthesia was induced with 10% chloral hydrate (300 mg/kg, intraperitoneal). The depth of anesthesia was monitored by observing muscle tone and the pedal withdrawal reflex. Then, lung ventilation was performed using a SAR-830A animal ventilator (CWE, Ardmore, PA, USA) for 3 hr of reperfusion (tidal volume: 6-8 mL/kg and respiratory rate: 80 breaths/min), during which ECG was conducted via ECG-6511 electrocardiograph (Nihon Kohden Corporation, Tokyo, Japan). After routine depilation and disinfection, incisions were made through the skin, superficial fascia, and deep fascia of the left chest. The pectoralis major and serratus anterior muscles were separated using hemostatic forceps. The third and fourth costal cartilages were then incised to expose the heart. The left coronary vein, along with the LAD, was identified between the left atrial appendage and the lung cone. The LAD was ligated 2 mm from the tip of the left atrial appendage for 30 min, and myocardial ischemia was confirmed by ST-segment elevation on the electrocardiogram. Reperfusion was then carried out for 3 hr, as evidenced by the change in color of the coronary artery and ST-segment depression on the electrocardiogram. Prior to reperfusion, 10 mg/kg lidocaine was intravenously injected in lidocaine group.

Measurement of cardiac function

At the conclusion of the reperfusion process, cardiac function in rats was evaluated. Measurements of LVSP and LVEDP were obtained using PowerLab C Data Acquisition - Life Science Data Acquisition (https://www.adinstruments.com/products/powerlab/c). Additionally, FS and EF were assessed strictly adhering to the manufacturer's instructions.

Determination of serum LDH and CK levels

After assessing cardiac function, a 5.0 mL blood sample was promptly drawn from the common carotid artery and centrifuged at 2,000 rpm for 15 min to separate the serum. The serum levels of LDH and CK were then measured using chemical colorimetry, following the protocol outlined in the kit instructions provided by Beyotime (Shanghai, China). This procedure ensured accurate and reliable determination of LDH and CK concentrations in the serum.

Measurement of MIS

To ensure precision, the procedure started with the withdrawal of blood, followed by euthanasia of the rats using an overdose of anesthesia. The heart was then swiftly removed and washed thoroughly with normal saline to clear any residual blood. Afterward, the LAD was ligated, and the heart was perfused with a 1% solution of Evans blue dye. The left ventricle was cut into 4-5 slices and stained with TTC for a duration of 15 min. These slices were analyzed with ImageJ 1.46 software (Version 1.38; National Institutes of Health, Bethesda, MA, USA) to delineate and quantify the non-ischemic zone (indicated by blue stain), the at-risk zone (which did not take up Evans blue dye), and the infarct zone (which did not stain with TTC). The size of the infarct (%) was determined by calculating the ratio of the infarcted area to the total myocardial area.

Western blotting

Following the harvesting of myocardial tissues, proteins were extracted using a modified RIPA buffer, and their concentrations were determined using BCA colorimetry. The proteins were separated on a 10% SDS-polyacrylamide gel via electrophoresis

and transferred to a nitrocellulose membrane. The membrane was blocked with a blocking solution at 37°C for 1.5 hr and washed three times with TBST. Subsequently, the membrane was incubated overnight at 4°C with primary antibodies: p-JNK at a dilution of 1:500, JNK at 1:1000, NF-κB at 1:1000, and GAPDH at 1:3000. After another round of washing with TBST three times, the membrane was incubated with horseradish peroxidase-labeled secondary antibodies at 37°C for 1 hr. The membrane was then washed three times with the blocking solution and three additional times with TBST. Finally, the membrane was stained and imaged for optical density analysis. The relative expression level of each target protein was quantified by calculating the ratio of its optical density to that of GAPDH.

HE staining

The myocardial tissues from each group were first stored in 10% formalin overnight, dehydrated, embedded in paraffin, sliced into 5 μm-thick sections, fixed on glass slides, baked dry and stained. The resulting sections were immersed successively in xylene, gradient concentrations of alcohol and hematoxylin in accordance with the relevant specifications, sealed using resin, dried in the air and observed and photographed under an optical microscope. Finally, the changes in the myocardial cell morphology, cardiac mesenchyme and myofilaments were observed.

TUNEL assay

To assess myocardial cell apoptosis, we utilized the TUNEL assay in accordance with the protocols outlined in the ApopTag Plus Peroxidase *in situ* Apoptosis Detection Kit (Chemicon, Millipore, Billerica, MA, USA). Initially, paraffin-embedded tissue sections, each with a thickness of 5 μm, were stained with hematoxylin. Subsequently, the quantification of TUNEL-positive cells was performed by examining five randomly selected fields per sample under a magnification of ×200.

Statistical analysis

Intergroup differences were evaluated using one-way analysis of variance, and Tukey's test was utilized for conducting multiple comparisons. The data were presented as mean values with their corresponding standard deviations. The threshold for statistical significance was established at a significance level of 0.05. Data analysis was performed using SPSS software version 20.0, developed by IBM and based in Armonk, NY, USA. A p-value of less than 0.05 was considered indicative of statistical significance.

RESULTS

Comparison of cardiac function

Following reperfusion, there was a significant decline in LVSP, FS, and EF, and a substantial increase in LVEDP in the reperfusion group compared to the sham group ($p<0.05$). In comparison with reperfusion group, lidocaine group had notably raised LVSP, FS and EF ($p<0.05$) and remarkably lowered LVEDP ($p<0.05$) (Table 1).

Influences of lidocaine on serum LDH and CK levels

After reperfusion, as illustrated in Figure 1, serum levels of both LDH and CK were significantly higher in the reperfusion group compared to the sham group ($p<0.05$), whereas lidocaine group had obviously lower levels of serum LDH and CK than reperfusion group ($p<0.05$).

Rat MIS determined

After reperfusion, the MIS was obviously increased in reperfusion group compared with that in sham group ($p<0.05$), while the MIS in lidocaine group was substantially smaller than that in reperfusion group (Figure 2).

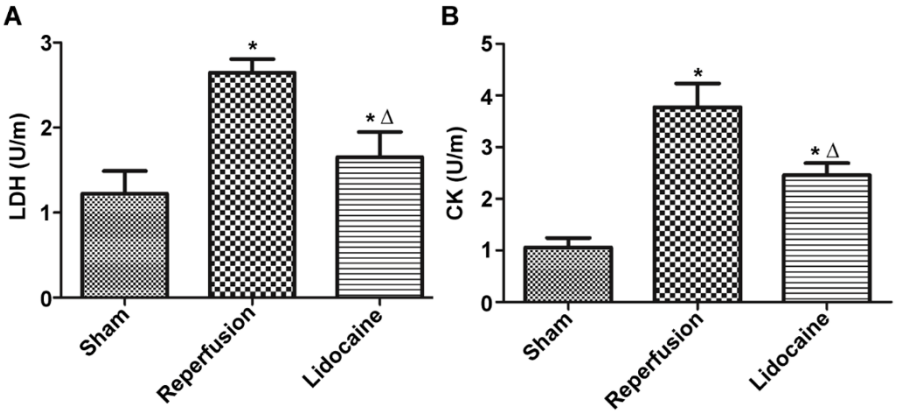

Figure 1: Comparison of serum LDH and CK levels between the sham, reperfusion, and lidocaine groups. The lidocaine group showed significantly lower levels compared to the reperfusion group (Δ$p<0.05$ vs. sham group, *$p<0.05$ vs. reperfusion group).

Comparisons of p-JNK and p-NF-κB protein levels in myocardial tissues

After reperfusion, reperfusion group had a substantially higher level of p-JNK (p<0.05) than sham group, while its level in lidocaine group was remarkably lower than that in reperfusion group (p<0.05). Conversely, the level of p-NF-κB in reperfusion group was significantly lower than that in the sham group (p<0.05). However, in the lidocaine group, its level was significantly higher compared to the reperfusion group (p<0.05) (Figure 3). To evaluate the microstructural changes of myocardial cells in the cross-section of the heart, HE staining was performed in the myocardial tissues. In reperfusion group, myocardial cells had obvious edema, and myofilaments were disorderedly arranged, with different degrees of degradation and necrosis and inflammatory cell infiltration. After lidocaine treatment, the edema in myocardial tissues was evidently mitigated, and myofilament abnormalities were significantly improved, suggesting that lidocaine treatment can relieve MIRI.

TUNEL assay results

Lidocaine inhibited myocardial cell apoptosis, and TUNEL-positive cells were obviously increased during reperfusion, implying that lidocaine can prevent myocardial cell apoptosis (Figure 4).

DISCUSSION

Cardiovascular disease remains the leading cause of deaths worldwide, especially in industrialized countries. Acute myocardial infarction causes ischemic injury and tissue necrosis mainly due to coronary artery occlusion.[11] At present, myocardial reperfusion by means of angioplasty or thrombolysis is the only approved therapy that can rescue ischemic myocardium and improve the prognosis of patients. However, such sudden reperfusion induces harmful secondary effects, known as IRI, aggravating ischemic damage and further increasing the infarct area.[12] The abrupt reverse flow of blood sets off a cascade of intricate intracellular processes. These include the generation of reactive oxygen species, disturbances in the balance of intracellular and mitochondrial functions, dysfunctions within the microcirculation, infiltration of inflammatory cells, accumulation of fluid leading to edema, and programmed cell death, or apoptosis. Collectively, these events contribute significantly to the death of myocardial cells affected by ischemia.[13] It was estimated that the area of IRI accounts for 25-50% of the total infarct area.[14] Therefore, it is vital to research MIR. The mechanism of MIRI has been researched extensively up to now, but it remains elusive.

JNK, a stress-activated protein kinase involved in inflammation, becomes phosphorylated in response to inflammatory stimuli. This phosphorylation event prompts the translocation of JNK

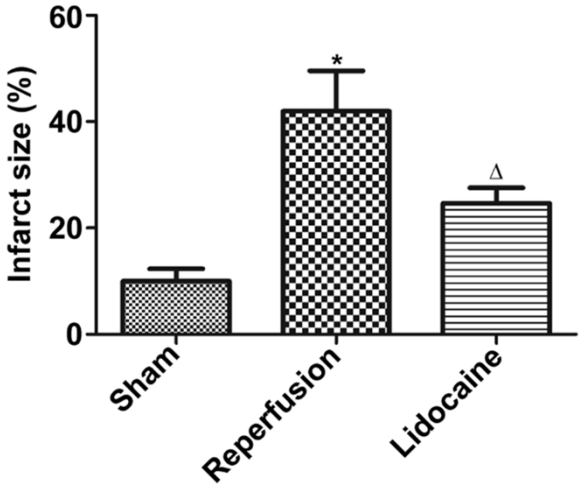

Figure 2: Myocardial Infarct Size (MIS) in sham, reperfusion, and lidocaine groups. Lidocaine treatment significantly reduced the MIS compared to the reperfusion group (Δp<0.05 vs. sham group, *p<0.05 vs. reperfusion group).

Table 1: Comparisons of cardiac function indexes among all groups.

Group	LVSP (mmHg)	LVEDP (mmHg)	FS (%)	EF (%)
Sham group	118.5±12.53	7.60±1.12	42.75±5.99	75.76±10.74
Reperfusion group	89.44±7.02$^{\Delta}$	10.58±1.02$^{\Delta}$	21.76±2.75$^{\Delta}$	40.28±5.49$^{\Delta}$
Lidocaine group	99.98±10.45$^{\Delta*}$	9.45±1.02$^{\Delta*}$	26.45±5.01$^{\Delta*}$	50.37±7.89$^{\Delta*}$

Note: Δp<0.05 vs. sham group, and *p<0.05 vs. reperfusion group.

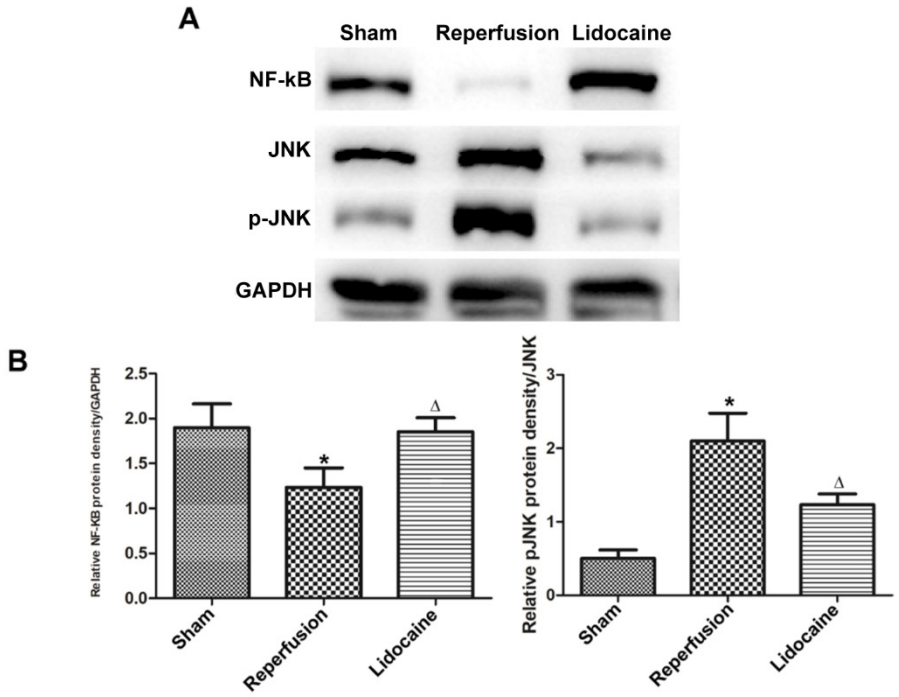

Figure 3: Expression levels of Phosphorylated JNK (p-JNK) and NF-κB in myocardial tissues across sham, reperfusion, and lidocaine groups. Lidocaine treatment significantly decreased p-JNK levels compared to the reperfusion group (Δp<0.05 vs. sham group, *p<0.05 vs. reperfusion group).

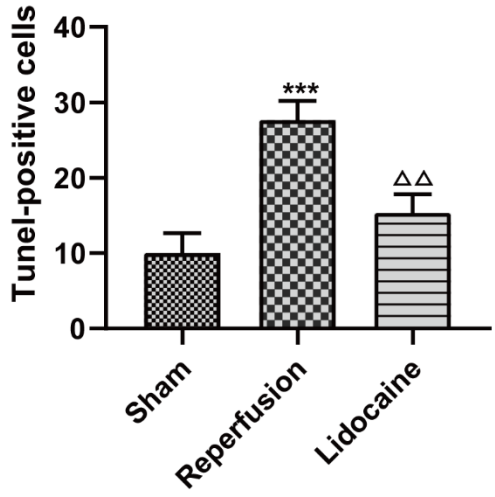

Figure 4: TUNEL assay results showing myocardial apoptosis levels in sham, reperfusion, and lidocaine groups. Lidocaine significantly reduced myocardial apoptosis compared to the reperfusion group (***p<0.001 vs. Sham group, ΔΔp<0.01 vs. Sham group).

into the nucleus, where it is involved in regulating the expression of pro-inflammatory cytokines such as TNF-α and IL-6.[15] As a member of the MAPK family, JNK is capable of modulating various cellular processes including proliferation, differentiation, and apoptosis,[16] and it is activated in response to various cell stresses, such as heat shock and ultraviolet radiation. Notably, JNK activation is observed in MIRI, unlike in ischemic conditions alone,[17] and this activation is associated with the activation and nuclear translocation of NF-κB.[18] It was previously evidenced that compared with those in wild-type mice, the MIRI-induced cell necrosis and apoptosis are mitigated in the mice with the knockout of JNK.[19] However, the relationship between the JNK pathway and MIRI has not yet been clarified. The present study corroborated the role of the JNK pathway in MIR and the influence of lidocaine on it.

Lidocaine, a commonly utilized local anesthetic and anti-arrhythmic medication, has been demonstrated to block sodium channels in myocardial cells, reduce the intracellular calcium load, decrease the production of ROS, and modulate mitochondrial bioenergy. These actions collectively contribute to its protective effects against MIRI.[20,21] The study using laboratory animals has suggested that systemic lidocaine can protect against MIRI,[22,23] but the mechanism by which lidocaine affects MII has been unclear. This study confirmed that lidocaine may exert an effect through the JNK pathway.

In this study, the rat MIR model was established, and the role of lidocaine in MIR was explored. According to the results, lidocaine group exhibited obviously higher LVSP, FS and EF, markedly lower LVEDP, substantially lower serum LDH and CK levels and notably smaller MIS than reperfusion group, suggesting that lidocaine can alleviate MIRI in rats. The current study's results indicated a marked rise in the levels of p-JNK in the reperfusion group when compared to the sham group. Notably, the expression of p-JNK in the lidocaine-treated group was even higher than

that observed in the reperfusion group. This observation suggests that the protective effect of lidocaine may be associated with its ability to inhibit the JNK signaling pathway.

This study has certain limitations. First, it used a single animal model, which may not fully replicate the complexity of human myocardial ischemia-reperfusion injury. Second, the sample size was relatively small, limiting the generalizability of the findings. Future research should include a larger sample size and explore the effects of lidocaine in different models and clinical settings to confirm its therapeutic potential.

CONCLUSION

In conclusion, this study demonstrates that lidocaine alleviates myocardial ischemia-reperfusion injury in rats by modulating the JNK signaling pathway, resulting in decreased activation of NF-κB and p-JNK.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

MIR: Myocardial ischemia-reperfusion; **LDH:** Lactate dehydrogenase; **CK:** Creatine kinase; **JNK:** c-Jun N-terminal kinase; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **WB:** Western blotting; **RT-PCR:** Reverse transcription-polymerase chain reaction; **HE:** Hematoxylin-Eosin: **MAPK:** Mitogen-activated protein kinase; **ERKs:** Extracellular signal-regulated kinases; **MIS:** Myocardial infarct size; **SD:** Sprague-Dawley; **RIPA:** Radio immuno precipitation assay; **BCA:** Bicinchoninic acid; **ECG:** Electrocardiography; **LAD:** Left anterior descending artery; **LVSP:** Left ventricular systolic pressure; **LVEDP:** Left ventricular end-diastolic pressure; **FS:** Fractional shortening; **EF:** Ejection fraction; **TTC:** 2,3,5-triphenyltetrazolium chloride; **SDS:** Sodium dodecyl sulfate; **TBST:** Tris buffered saline-tween; **p-JNK:** Phosphorylated JNK; **GAPDH:** glyceraldehyde-3-phosphate dehydrogenase; **SPSS:** Statistical Product and Service Solutions.

AUTHORS' CONTRIBUTIONS

Jie Qi, Xiangkong Song and Yuxia Gao designed the study and performed the experiments, Qianqian Yang and Qingtan Zhang collected the data, Qianqian Yang, Qingtan Zhang and Meiling Liu analyzed the data, Jie Qi, Xiangkong Song and Yuxia Gao prepared the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Animal Ethics Committee of Tianjin Medical University Animal Center.

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