Original Article

Mechanism of ATP-sensitive potassium channel opener natalin kalin to improve congestive heart failure after myocardial infarction

Jianguo Zhao¹, Xuelian Feng¹, Qinghua Zhang², Gang Liu³

¹Department of Cardiology, Zouping Central Hospital, Binzhou 256212, Shandong, China; ²Qingdao Women’s and Children’s Hospital, Qingdao 266000, Shandong, China; ³Zouping Central Hospital, Zouping, Binzhou 256212, Shandong, China

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Abstract: Natakalim, an agonist that targets ATP-sensitive potassium channel ($k_{ATP}$) activity on vascular endothelial cells and myocardial cells, interferes with acute myocardial infarction (AMI) and secondary congestive heart failure (CHF) rats. The effect of the model and related molecular mechanisms would lay the theoretical foundation for improving clinical prognosis of AMI secondary CHF by natakalim. After grouping and experimental results, we show $k_{ATP}$ activity on vascular endothelial cells and myocardial cells. It greatly participates in the channel activation, natacarin can activate $k_{ATP}$ channels, improve vascular endothelial cell hypoxia damage, inhibit myocardial cell inflammation and apoptosis, and may mediate the MAPK signaling pathway phosphate. Thus it may be related pharmacological mechanisms.

Keywords: ATP-sensitive potassium channel, natalin, acute myocardial infarction, congestive heart failure, hypoxia-inducible factor-1, heat shock protein-70, inflammatory factor, apoptosis, MAPK signaling pathway

Introduction

Acute myocardial infarction (AMI) is one of the most common diseases resulting in congestive heart failure (CHF) in clinical practice. It is the main pathological change from acute ischemia-anoxia injury of the coronary artery and results in apoptosis or necrosis of cardiomyocytes in the innervation area. The dysfunction of vascular endothelial cells and cardiomyocytes is the key link in the occurrence of CHF in AMI [1, 2]. Previous studies have suggested the relationship between AMI, secondary CHF and neuro-endocrine dysfunction, vascular endothelial injury, atheromatous plaque formation and secondary lesions. The inflammatory response is related to oxidative stress disorder, and other mechanisms affecting vascular endothelial cells and myocardial cell dysfunction.

ATP-sensitive potassium channels ($K_{ATP}$) are important channels for regulating potassium concentrations in eukaryotic cells and also the sodium potassium pump. It is related to the difference in ATP concentration gradients inside and outside the membrane. It belongs to the category of inward rectifier potassium channels found in the heart, where smooth muscle cells, endothelial cells, etc. are abundantly distributed [3, 4]. Under the condition of ischemia and hypoxia, $K_{ATP}$ functioning is most susceptible, resulting in abnormal energy metabolism of vascular endothelial cells and cardiomyocytes, which in turn affects the survival state of cells. $K_{ATP}$ is the only ion channel coupled with cell metabolism and cell membrane potential. It is basically in a closed state under physiological conditions. $K_{ATP}$ is abnormally activated when cells are hypoxic, and energy metabolism is disordered, and potassium influx is increased. Indirect or direct promotion of sodium outflow, significantly affects the pathophysiological process of diseases like hypertension, myocardial ischemia and heart failure, and is a promising target for the intervention in cardiovascular disease [5, 6]. $K_{ATP}$ consists of two parts: the inward rectifier potassium channel (Kir) and the sulfonylurea receptor (SUR). The former forms ion channels, and the latter determines functional expression. $K_{ATP}$ on the cardiomyocyte
membrane is a subtype of SUR2A/Kir6.2, and on the endothelial cells is a subtype of SUR2B/Kir6.1 [7]. By selectively activating K_{ATP} subtypes on cardiomyocytes or endothelial cells, cell function can be corrected, anti-ischemic ability can be enhanced, reperfusion injury can be reduced, and cardiac remodeling progress can be delayed. Natalaline is a novel K_{ATP} channel opener that targets the activation of the SUR2B/Kir6.1 subtype and affects endothelial function [8]. Previous studies have shown that it has a better expression in anti-congestive heart failure, which can reverse the ventricular remodeling of the pressure overload animal model caused by abdominal aortic constriction [9].

Based on this, the study further explored the effect and related molecular mechanisms of the open-agent natakarin drug in the vascular secondary endothelial cells and cardiomyocytes targeting k_{ATP} activity in the AMI secondary CHF rat model. Carlin provides a theoretical basis for improving the clinical prognosis of AMI secondary CHF.

Materials and methods

Animal source and model establishment

A total of 30 healthy 8-week-old Sprague-Dawley rats were selected, with an average body weight of (330±35) g, including both males and females. They were purchased from Shanghai Biotechnology Animal Experimental Center. Their care followed standard animal feeding and experimental principles, and were kept in normal environment for 1 week.

The AMI model was created through the methodology of the left anterior descending coronary artery ligation. The plasma BNP level was determined to be at least 2 times higher than the reference level for CHF model after 4 weeks of feeding. The control group did not have ligation of the left anterior descending artery. The main steps were: rat weighing, anesthesia induction with pentobarbital (40 mg/kg) intraperitoneal injection, tracheal intubation, small animal respirator, ECG electrode needle buried in the limbs of rats, recording ECG. Cut the skin along the left sternum, open the chest, expose the heart, remove the happy bag from the ophthalmology, and use the 7-0 non-invasive suture needle to pass through the left coronary artery 2 mm from the beginning of the left anterior reducing coronary artery between the pulmonary artery cone and the left atrial appendage. Anterior descending branch ligation. Immediately, the ST segment of ECG II lead was what elevated, the ligation area became white, and the pulsation weakened, which proved that the AMI model was successfully constructed. The chest was closed, the thoracic gas and drainage exudate were taken, and the chest was closed layer by layer. The tracheal intubation was removed, the skin was sutured, and penicillin was used to prevent infection after surgery. The normal environment was kept sterile for 4 weeks, and the plasma BNP level was detected by radioimmunoassay. When BNP was at least 2 times higher than the reference level, the CHF model was successfully constructed. The BNP test kit was purchased from Jiangsu Biyuntian Technology Co., Ltd. After 8 weeks, the rats were sacrificed and the hearts were removed. Three groups of vascular endothelial cells and left ventricular cardiomyocytes were randomly selected from each group. Other than the control group, the other groups were constructed with AMI secondary CHF model, and the natakarin and ATPase inhibitors were provided by the Beijing Saidweikang Research Institute.

Experimental grouping and observation indicators

Thirty rats were randomly arranged into 5 groups including control group, model group, natakaline 3 mg/kg/d group, nakacarin 9 mg/kg/d group, sodium potassium pump ATPase inhibitor 3 mg/kg/d group. There were 6 rats in each group. Other than the control group, the other groups were constructed with AMI secondary CHF model, and the natakarin and ATPase inhibitors were provided by the Beijing Saidweikang Research Institute.

Western blot method

The sample cells of each experimental group were first subjected to ultrasonic high-speed
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Table 1. Purpose Primer sequence and size

<table>
<thead>
<tr>
<th>Target primer</th>
<th>Forward sequence</th>
<th>Reverse sequence</th>
<th>Size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>5′-ATATGGGCAGCATC-3′</td>
<td>5′-CTCTATGGAACCTTG-3′</td>
<td>165</td>
</tr>
<tr>
<td>TNF-α</td>
<td>5′-GGCCGCCTTTAAAA-3′</td>
<td>5′-CCGGTTTTGGGCCA-3′</td>
<td>198</td>
</tr>
<tr>
<td>caspase-3</td>
<td>5′-TACGATGGGCGCGACTTC-3′</td>
<td>5′-TACGATGGGCGCGACTTC-3′</td>
<td>103</td>
</tr>
<tr>
<td>bcl-2</td>
<td>5′-ACTACCTCCGGCGCTAC-3′</td>
<td>5′-GAATCAACAGGGCCGCTATG-3′</td>
<td>332</td>
</tr>
<tr>
<td>bax</td>
<td>5′-GGTTCTACGAGGCGCCACGAG-3′</td>
<td>5′-CAAAAGATGGTACGTCGCC-3′</td>
<td>445</td>
</tr>
<tr>
<td>Internal reference gapdh</td>
<td>5′-CGCGAGAAGATGCACCAGAT-3′</td>
<td>5′-GCACGTGTTGCGGTACAG-3′</td>
<td>225</td>
</tr>
</tbody>
</table>

lys, and the protein concentrations of extracted cell proteins were assayed by BCA protein quantification kit (American R&D Company); 30 μg of sample protein was taken from each group and run on 8% SDS-PAGE electrophoresis. The total proteins were transferred to a PVDF membrane by electrical current; the rabbit anti-rat SUR2B/Kir6.1 subtype, HIF-1, HSP-70, p-MAPK and internal reference β-actin antibody. Primary antibodies (from Sigma USA) were added dropwise (concentration was 1: 2000 after dilution) and allowed to stand overnight; after washing with PBS, the goat anti-rabbit corresponding secondary antibody (diluted 1:500, diluted sigma) was incubated for 4 h at room temperature; washed with PBS, and developed by ECL (American Sigma). The results were expressed by the gray scale ratio of the electrophoresis bands of the target protein and the internal reference protein, and densitometrical analysis was acquired with the aid of Lab Works 4.5 gel imaging software (Invitrogen, USA).

Reverse transcription PCR (RT-PCR) method

The sample cells of each experimental group were first subjected to high-speed ultrasonic lysis, and the total RNA was extracted by one-step method using Trizol reagent (CA), and the RNA concentration and quality was measured. The reverse transcription system was performed according to the reverse transcription kit (Invitrogen, USA). Synthetic cDNA was synthesized by adjusting the amplification parameters; the target primer sequence was synthesized by Shanghai Biotech Co., Ltd. according to the Gene Bank sequence (Table 1), and the electrophoresis amplification reaction system was cDNA 2 μl + upper and lower primers, 3 μl each + Taq polymerase 0.5 μl, and sterilized. The reaction volume was brought to a total volume of 25 μl, and the reaction conditions were 95°C for 5 min, (95°C 30 s, 58°C 30 s, 72°C 60 s) for 30 amplification cycles, 72°C for 10 min. Finally, the PCR product was identified, and the gel imaging analysis system was used for semi-quantitative analysis. The results were expressed by the gray scale ratio of the electrophoresis bands of the target primer and the internal reference primer.

Tunel method

Coronary endothelium and myocardial tissue sections were prepared by conventional methods with a thickness of 4 μm; and detected by Roche kit. The main steps are as follows: the tissue sections are fully dewaxed to hydration treatment, soaked with hydrogen peroxide formaldehyde, and proteinase K (20 μg/ml) is dissolved in Tris/Hcl solution (pH 7.4~8.0) for 15 min at room temperature; PBS is washed and sucked dry, the reaction mixture was added with 50 μl and incubated in a wet box at 37°C for 60 min, and then coverslipped; wash with PBS, measure the percentage of green labeled cells under fluorescent microscope; then add 50 μl of transformant to the wet box. Incubate at °C for 20 min, cover the coverslip; wash with PBS, add 50 μl of DAB substrate solution and incubate for 10 min at room temperature (10~25°C); wash with PBS, stain with hematoxylin for 1~3 s, and seal with neutral gum.

Results: Five fields from the upper, middle, lower, left and right were randomly selected. A total of 100 total cells were counted under a 300-fold fluorescence microscope, and the percentage of positive cells was calculated as the apoptotic rate.

Statistical methods

In the statistical analysis, SPSS 20.0 software was adopted. Mean ± standard deviation was applied to express the measurement data. According to the experiment, it was divided into 5 groups to compare the expression of SUR2B/Kir6.1 subtype, HIF-1, HSP-70 protein, and IL-6. TNF-α, caspase-3, bax/bcl-2 mRNAs expres-
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**Results**

Relative expression levels of SUR2B/Kir6.1 subtype, HIF-1 and HSP-70 proteins in vascular endothelial cells of each group

First, ANOVA analysis was used to find that there was significant difference among the groups (F = 25.326, P<0.001); then further comparison between the two subgroups revealed that the relative expression of the SUR2B/Kir6.1 subtype protein expression did not show significant difference in the model group compared with that in the control group (F = 0.869, P = 0.325). Compared with the control group and the model group, the relative expression of SUR2B/Kir6.1 subtype protein in the 3 mg/kg/d and 9 mg/kg/d groups was significantly increased (Natacarin 3 mg/kg/d group compared with control group, F = 18.536, P<0.001; Natacarin 3 mg/kg/d group compared with model group, F = 15.632, P<0.001; Natacarin 9 mg/kg/d group by comparison with control group, F = 20.236, P<0.001; Natacarin 9 mg/kg/d group by comparison with model group, F = 17.528, P<0.001). The comparison between the 9 mg/kg/d groups was not significant (F = 0.659, P = 0.427). Relative to the control group and the model group, the ATPase inhibitor group was the smallest (F = 5.639, 6.538, P<0.001).

Compared with the control group, the similar observation found that the relative expression levels of HIF-1 and HSP-70 proteins in the model group were significantly elevated, while those in the 3 mg/kg/d and 9 mg/kg/d natacarin groups were lower than those in the model group, and the ATPase inhibitors. The group was higher than the model group (P<0.001). The above indicators were not significantly different between the 3 mg/kg/d and 9 mg/kg/d groups (P<0.001) (Figures 1, 2).

Relative expression levels of IL-6, TNF-α, caspase-3 and bax/bcl-2 mRNAs in myocardial cells of each group

First, ANOVA analysis was used to determine that the differences between the groups were significant (IL-6: F = 56.326, P<0.001; TNF-α: F = 52.325, P<0.001; caspase-3: F = 48.965, P<0.001; bax/bcl-2: F = 68.625, P<0.001); then further comparison between the two subgroups found that the IL-6, TNF-α, caspase-3, and bax/bcl-2 mRNAs in the model group were significantly increased by comparison with the counterparts in the control group, Nata Carlin 3 mg/kg/d group and 9 mg/kg/d group were reduced by comparison with the model group, and ATPase inhibitor group was induced by comparison with the model group (P<0.05). The above indicators were in the 3 mg/kg/d group and The difference between the 9 mg/kg/d groups was not detected (P<0.05) (Table 2).

Apoptosis rate and relative expression of p-MAPK protein in each group of cardiomyocytes

First, ANOVA analysis was used to find that there were significant differences between groups (F = 55.632, 42.235, and 39.639, all P<
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Comparison of plasma BNP levels in each group

Immediately after modeling, significant difference was observed among the groups (F = 45.569, P<0.001). By comparison with the control group, the plasma BNP levels in the other groups increased significantly (P<0.001), however, no difference was found among the other groups (P>0.05). After 8 weeks of culture, significant difference did not disappear among the groups (F = 102.326, P<0.001), and further comparison between subgroups, by comparison with the control group, the other groups were significantly increased (P<0.001), compared with the model group. The plasma BNP levels in the 3 mg/kg/d and 9 mg/kg/d groups were significantly reduced, while the ATPase inhibitor group was increased (P<0.001), and the 3 mg/kg/d and 9 mg. No clear difference was detected among the groups per kg/d (P<0.05).

Compared with the model immediately after 8 weeks of culture in each group, only the control group stabilized at the level (t = 0.562, P = 0.423), and the other groups increased significantly (P<0.001) (Table 4).

Discussion

Myocardial ischemia, especially AMI, is the main cause of CHF. Therefore, this study constructed a rat model of AMI secondary CHF. By detecting electrocardiogram and plasma BNP levels, AMI and CHF can be accurately judged, and the stability of the model can be judged by observing the activity ability of the rat. The operation is simple, the survival rate of the rat is high, and the experiment can be successfully completed [10]. This experiment compared the effects of natacarbin 3 mg/kg/d group and 9 mg/kg/d group and ATPase inhibitor group on $K_{ATP}$ activity; setting natakaline 3 mg/kg/d and 9 mg/kg/d is based on previous experiments found that the open activity of $K_{ATP}$ is related to the amount of $K_{ATP}$ and the concentration of opener. The open activity of $K_{ATP}$ is positively correlated with the concentration of opener in a certain range, and natakaline 3 mg/kg/d is the fastest change in $K_{ATP}$ open activity, and the highest open activity at 9 mg/kg/d [11]. ATPase inhibitors can specifically antagonize sodium potassium pump activity and reduce $K_{ATP}$ open activity to some extent [12].
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and HSP-70 protein in the model group was significantly elevated. By comparison with the model group, the natakarin 3 mg/kg/d group and the 9 mg/kg/d group were reduced, and the ATPase inhibitor group was elevated by comparison with the model group (P<0.05). The above indicators were not significantly different between the 3 mg/kg/d group and the 9 mg/kg/d group of natakalamin (P<0.05). It is suggested that the application of natakalamin can significantly enhance the open activity of K\textsubscript{ATP} and decrease the expression of HIF-1 and HSP-70 protein. Although there are many ways to affect cell metabolism, K\textsubscript{ATP} is widely distributed in vascular endothelial cells, smooth muscle cells and cardiomyocytes, and is susceptible to various factors inside and outside the receptor, especially ischemia, hypoxia, inflammation and oxidation stress, metabolic disorders, etc [13]. In AMI or CHF, K\textsubscript{ATP} activity tends to be downregulated, which in turn induces the release of a large number of vasoconstrictors such as

Table 2. Relative expression levels of IL-6, TNF-\alpha, caspase-3 and bax/bcl-2 mRNAs in cardiomyocytes of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-6</th>
<th>TNF-\alpha</th>
<th>caspase-3</th>
<th>bax/bcl-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>0.12ro.03</td>
<td>0.09ro.03</td>
<td>0.08ro.03</td>
<td>0.24ro.03</td>
</tr>
<tr>
<td>Model group</td>
<td>0.36ro.03</td>
<td>0.32ro.03</td>
<td>0.29ro.03</td>
<td>0.57ro.03</td>
</tr>
<tr>
<td>Natalaline 3 mg/kg/d group</td>
<td>0.24kg/d\textsuperscript{a,b}</td>
<td>0.20kg/d\textsuperscript{a,b}</td>
<td>0.17kg/d\textsuperscript{a,b}</td>
<td>0.35kg/d\textsuperscript{a,b}</td>
</tr>
<tr>
<td>Natalaline 9 mg/kg/d group</td>
<td>0.23kg/d\textsuperscript{a,b}</td>
<td>0.19kg/d\textsuperscript{a,b}</td>
<td>0.16kg/d\textsuperscript{a,b}</td>
<td>0.34kg/d\textsuperscript{a,b}</td>
</tr>
<tr>
<td>ATP enzyme inhibitor group</td>
<td>0.42enzym\textsuperscript{a,b,c,d}</td>
<td>0.36enzym\textsuperscript{a,b,c,d}</td>
<td>0.33enzym\textsuperscript{a,b,c,d}</td>
<td>0.68enzym\textsuperscript{a,b,c,d}</td>
</tr>
</tbody>
</table>

F                  | 56.325    | 52.325     | 48.965    | 68.625    |
P                  | 0.000     | 0.000      | 0.000     | 0.000     |

Note: a By comparison with the control group, P<0.05; b By comparison with the model group, P<0.05; c By comparison with the natakarin 3 mg/kg/d group, P<0.05; d And The natacarbin 9 mg/kg/d group was determined, P<0.05.

Table 3. Apoptosis rate and relative expression of p-MAPK protein in each group of cardiomyocytes

<table>
<thead>
<tr>
<th>Group</th>
<th>Apoptosis rate (%)</th>
<th>MAPK</th>
<th>p-MAPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>0.09ro.03</td>
<td>0.22ro.07</td>
<td>0.15ro.07</td>
</tr>
<tr>
<td>Model group</td>
<td>0.35ro.03</td>
<td>0.42ro.03</td>
<td>0.30ro.03</td>
</tr>
<tr>
<td>Natalaline 3 mg/kg/d group</td>
<td>0.24kg/d\textsuperscript{a,b}</td>
<td>0.29kg/d\textsuperscript{a,b}</td>
<td>0.23kg/d\textsuperscript{a,b}</td>
</tr>
<tr>
<td>Natalaline 9 mg/kg/d group</td>
<td>0.23kg/d\textsuperscript{a,b}</td>
<td>0.28kg/d\textsuperscript{a,b}</td>
<td>0.22kg/d\textsuperscript{a,b}</td>
</tr>
<tr>
<td>ATP enzyme inhibitor group</td>
<td>0.44y enzym\textsuperscript{a,b,c,d}</td>
<td>0.48y enz y\textsuperscript{a,b,c,d}</td>
<td>0.39y enz y\textsuperscript{a,b,c,d}</td>
</tr>
<tr>
<td>F</td>
<td>55.635</td>
<td>42.235</td>
<td>39.639</td>
</tr>
</tbody>
</table>
P                  | 0.000               | 0.000       | 0.000     |

Note: a By comparison with the control group, P<0.05; b By comparison with the model group, P<0.05; c By comparison with the natakarin 3 mg/kg/d group, P<0.05; d And The natacarbin 9 mg/kg/d group was compared, P<0.05.

Table 4. Comparison of plasma BNP levels in each group (pg/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Immediately after modeling</th>
<th>After 8 weeks of cultivation</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>6</td>
<td>12.6ro.01</td>
<td>12.9ro.01</td>
<td>0.562</td>
<td>0.423</td>
</tr>
<tr>
<td>Model group</td>
<td>6</td>
<td>56.8ro.01</td>
<td>82.6ro.01</td>
<td>35.632</td>
<td>0.000</td>
</tr>
<tr>
<td>Natalaline 3 mg/kg/d group</td>
<td>6</td>
<td>56.7kg/d\textsuperscript{a}</td>
<td>62.2kg/d\textsuperscript{a,b}</td>
<td>6.569</td>
<td>0.001</td>
</tr>
<tr>
<td>Natalaline 9 mg/kg/d group</td>
<td>6</td>
<td>57.3kg/d\textsuperscript{a}</td>
<td>61.9kg/d\textsuperscript{a,b}</td>
<td>6.458</td>
<td>0.001</td>
</tr>
<tr>
<td>ATP enzyme inhibitor group</td>
<td>6</td>
<td>57.5y enzym\textsuperscript{a}</td>
<td>102.8y enz y\textsuperscript{a,b,c,d}</td>
<td>65.828</td>
<td>0.000</td>
</tr>
<tr>
<td>F</td>
<td>45.569</td>
<td>102.326</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
P                  | 0.000             | 0.000                      |                               |     |     |

Note: a compared with the control group, P<0.05; b compared with the model group, P<0.05; c compared with the natakarin 3 mg/kg/d group, P<0.05; d And The natacarbin 9 mg/kg/d group was compared, P<0.05.
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endothelin, induces smooth muscle cell contraction, and induces cardiomyocyte apoptosis or necrosis [14]. The open-agent natalarin can specifically act on $K_{ATP}$, activate the closed potassium channel to re-open, induce $K_{ATP}$ to polymerize or depolymerize with the corresponding ligand, thereby activating downstream related signaling pathways, and transducing extracellular signals. In the mitochondria, from the cytoplasm to the nucleus, initiation of nuclear transcription factors, regulating of the expression of genes and proteins compatible with ischemia and hypoxia [15, 16]. HIF-1 and HSP-70 proteins are a type of damage repair molecule expressed by eukaryotes in an ischemic and hypoxic environment. High levels of HIF-1 and HSP-70 expression can also be detected in peripheral blood of patients with AMI or CHF in humans, suggesting that $K_{ATP}$ channel activity is closely related to HIF-1 and HSP-70 protein expression [17, 18].

It was further found that the transcriptional levels of IL-6, TNF-α, caspase-3, bax/bcl-2 mRNAs, apoptotic rate and p-MAPK protein in the model group were significantly increased by comparison with the counterparts in the control group, and natakarin 3 mg/kg/d. The group and the 9 mg/kg/d group were lower than the model group, and the ATPase inhibitor group was reduced by comparison with the model group (P<0.05). The above indicators were not significantly different between the 3 mg/kg/d group and the 9 mg/kg/d group of natakarin (P<0.05). It is suggested that the application of natakarin can reduce the degree of heart failure and even affect the process of ventricular remodeling and heart failure [22].

In summary, $K_{ATP}$ activity in vascular endothelial cells and cardiomyocytes greatly contributes to the occurrence and progress of AMI secondary CHF, and the target open-agent natalin can activate $K_{ATP}$ and improve vascular endothelial cell hypoxia injury, inhibition of cardiomyocyte inflammation and apoptosis. It may also mediate the pharmacological mechanism of MAPK signaling pathway phosphorylation.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Gang Liu, Zouping Central Hospital, No. 411 Qinghe 1st Road, Weiqiao, Zouping, Binzhou 256212, Shandong, China. E-mail: liugang191104@163.com

References


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