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用分子轨道计算方法研究儿茶素对自由基的清除作用

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提要 本文用分子轨道法计算了儿茶素分子各原子的本征向量、净电荷和电子分布等。发现当儿茶素与自由基反应时，苯并吡喃平面苯环上两个羟基比另一个苯环上的两个羟基活泼。

关键词 儿茶素；抗氧化剂；自由基清除剂；分子结构

清除作用，

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Effect of cimetidine on isolated rat myocardial reperfusion injury[1]

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ABSTRACT The effects of cimetidine (Cim) on ventricular fibrillation threshold (VFT), diastolic excitation threshold (DET), effective refractory period (ERP), and vulnerable period (VP), were determined in both stable perfusion and postischemic reperfusion rat hearts. The results showed that reperfusion after 15 min global myocardial ischemia caused a significant decrease VFT and ERP, and an increase in VP and DET. Cim 1 mmol · L^{-1} prevented the lowering in VFT, shortening in ERP, and lengthening in VP from the postischemic reperfusion. Cim 0.1 mmol · L^{-1} attenuated the exacerbation of VFT and VP. Cim 0.01 mmol · L^{-1} did not exert any noticeable influence on the electrophysiological parameters. It was shown that Cim 1 mmol · L^{-1} protected myocardium against the aggravation of electrophysiological characteristics induced by postischemic reperfusion.

KEY WORDS ventricular fibrillation; electrophysiology; cimetidine; myocardial reperfusion injury

Serious arrhythmias even as ventricular fibrillation (VF) are frequently induced by postischemic reperfusion[1]. A mass of histamine release is probably an important factor in the appearance of arrhythmias[2]. It has been proved that cimetidine, an H_2–receptor antagonist, has an anti–arrhythmia action during ischemia[3]. Nevertheless, the effects of Cim on reperfusion arrhythmias and its related mechanism are still uncertain. Furthermore, so far very few reports[4] have been found about the action of Cim on myocardial electrophysiological characteristics during reperfusion, this study was to investigate in isolated rat hearts whether Cim could prevent myocardial reperfusion changes.

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MATERIALS AND METHODS

Cim was obtained from Shanghai First Pharmaceutical Factory.

Wistar rats were bred from the Experimental Animal Center of Zhejiang Medical University.

ZMUP–1 computerized measuring apparatus for electrophysiological parameters was made by the subsidiary factory of Zhejiang Medical University.

Preparation of isolated hearts Forty–six rats weighing 230 ± *s* 21 g were used.

After ip heparin 250 IU, the heart was rapidly excised and mounted on a Langendorff perfusion apparatus. The heart chamber was jacketed by circulating water (37.5℃). Perfusion was carried out at 5 ml · min^{-1} · g^{-1} myocardium with modified Krebs–Hensleit (K–H) solution containing (mmol · L^{-1}): NaCl 118; KCl 4.7; KH_2PO_4 1.2; $MgSO_4$ 1.2; $NaHCO_3$ 25; $CaCl_2$ 1.23; glucose 11 aerated with 95% O_2+5% CO_2 at 37℃, pH 7.4. The epicardiogram was recorded by inserting a pair of stainless steel electrodes into left ventricular myocardium. The heart was paced at 5 hz with a strength of twice diastolic threshold of square wave current pulses via a pair of pacing electrodes in the free wall of right ventricle. The triggering electrodes were placed in the left ventricular wall. · Epicardiogram record was monitored throughout the experiments.

Measurement of cardiac electrophysiological characteristics

1 Ventricular fibrillation threshold (VFT) VFT was estimated by a train of pulse stimuli consisting of 10 square pulse waves of 5–ms duration and 2–ms interval. The heart was stimulated within the total duration of T wave. VF was defined as completely irregular QRS complex persisted for more than 6 cycles. The lowest value in milliampere (ma) required to produce VF was defined as VFT.

2 Diastolic excitation threshold (DET) A single pulse with awidth of 2 ms, delivered in the diastolic period of cardiac cycle, was used to test the DET. The minimal current in ma of the pulse that could induce premature systole was regarded as DET.

3 Effective refractory period (ERP) ERP was measured by the extra stimulation technique with a single stimulus, set at twice the DET, delivered at shorter coupling intervals in decrements of 2 ms until failure to capture. ERP was taken as the longest interval when failure to capture occurred.

4 Vulnerable period (VP) A single pulse with a width of 4 ms and an intensity of 1 ma above VFT was used to scan the interval between QRS complex and T wave with a step of 2 ms. The start and the end of VP were defined by the first and the last VF respectively. All these cardiac electrophysiological parameters were measured by the micro–computerized apparatus automatically.

Experimental protocol Rats were randomly divided into 4 groups: control (K–H solution), Cim 0.01, 0.1, and 1 mmol · L^{-1}. Measure the data of VFT, DET, ERP, and VP in every heart of four groups a after 30–min equilibration period. Global myocardial ischemia was induced by discontinuing perfused flow. Reperfusion was commenced after 15–min ischemia. Data were expressed as $\bar{x} \pm s$ for each group and comparisons were made between by "random squared difference analysis" and within each group by paired t test.

RESULTS

During early reperfusion period after 15–min global ischemia the lowering of VFT, elevating of DET, shortening of ERP, and the lengthening of VP appeared in the control group ($P<0.01$ *vs* perfusion, Tab 1). Cim 0.01, 0.1, and 1 mmol · L^{-1} did not have any significant effect to all electrophysiological parameters after 30–min equilibration perfusion. Yet Cim 1 mmol · L^{-1} exerted a preventive effect on the lowering of VFT, shortening of ERP and lengthening of VP induced by reperfusion ($P<0.01$ *vs* control). Owing to this effect, the differences of these parameters between perfusion period and reperfusion period were notably attenuated. However, Cim 1 mmol · L^{-1} did not have any significant effect on reperfused DET. Cim 0.1 mmol · L^{-1} only reduced the reperfused VFT lowering and VP

Tab 1. Effects of cimetidine on electrophysiological characteristics in isolated ischemic and reperfused rat hearts. ($\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **control**; $^{+}P>0.05$; $^{++}P<0.05$; $^{+++}P<0.01$ *vs* **perfusion**)

	Control	Cimetidine / mmol · L^{-1} 0.01	0.1	1
	12 rats	10 rats	12 rats	12 rats
Ventricular fibrillation threshold / ma				
Perfusion	3.73 ± 1.33	$3.98 \pm 1.51^{*}$	$3.70 \pm 0.88^{*}$	$4.23 \pm 0.81^{*}$
Reperfusion	$0.64 \pm 0.42^{+++}$	$0.74 \pm 0.41^{*+++}$	$2.85 \pm 0.74^{***--}$	$3.45 \pm 0.63^{***++}$
Diastolic excitation threshold / ma				
Perfusion	0.35 ± 0.12	$0.33 \pm 0.11^{*}$	$0.38 \pm 0.15^{*}$	$0.31 \pm 0.12^{*}$
Reperfusion	$0.56 \pm 0.22^{+++}$	$0.46 \pm 0.16^{*+++}$	$0.59 \pm 0.20^{*+++}$	$0.49 \pm 0.15^{*++}$
Effective refractory period / ms				
Perfusion	58.5 ± 13.3	$57.8 \pm 17.2^{*}$	$58.5 \pm 16.3^{*}$	$65.8 \pm 9.2^{*}$
Reperfusion	$29.5 \pm 9.8^{+++}$	$44.6 \pm 18.7^{*+--}$	$40.0 \pm 12.3^{*+++}$	$53.3 \pm 8.9^{***++}$

prolongation, but the effect was much weaker than that of Cim 1 mmol · L^{-1}. Cim 0.01 mmol · L^{-1} did not exert any effect on all these parameters.

DISCUSSION

This study showed that during early reperfusion the changes of myocardial electrophysiological characteristics were present, which was in accordance with some other authors[1,5]. Since Parameters of VFT, DET, ERP, and VP were regarded as the indices for myocardial electrophysiological stability, they reflected the possibility of the occurrence of arrhythmia directly. Thus, every change in these electrophysiological characteristics was closely related to the reperfusion arrhythmias[6,7].

In this paper it was shown that Cim could protect the myocardium against reperfusion-induced damage in the isolated rat heart and the effect was dependent on Cim concentration. This would provide evidence for the production of histamine during reperfusion. A mass release of histamine might play an important role in the genesis of reperfusion arrhythmias[2]. There were some explanations for histamine-induced damage to myocardial electrophysiology. Some experiments showed that histamine promoted inward calcium (Ca) current, increase intracellular Ca concentration and shorten the duration of action potential[8]. Others suggested that histamine slowed down the conduction in myocardium and accelerated autorhythmicity, so excitation reentry could be induced by histamine[9]. These might be the mechanism of electrophysiological changes and arrhythmias evoked by histamine. Since H_2-receptors are widely distributed in the sinoatrial node, the atria and the ventricles, myocardial damage due to histamine is closely related to H_2-receptors[10,11]. Cim blocks the H_2-receptors, so that it is able to protect myocardium against histamine induced damage.

The amounts of histamine contained in the hearts are different in various kinds of mammals. The content in rat heart is less than that in guinea-pig's[12]. Normal cardiac rhythm were recovered spontaneously from induced VF just in rat hearts, which offers an important advantage for our experiment. It is the very reason why rat was served as the experiment animal in this study.

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西咪替丁对离体鼠心缺血后复灌期电生理特性的保护作用

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提要 在离体灌流鼠心用微机程控测定证实复灌期心肌发生室颤阈(VFT)降低, 舒张阈(DET)升高, 不应期(ERP)缩短和易损期(VP)延长等损害性变化. 西咪替丁(Cim) 1 mmol · L^{-1} 显著抑制复灌期 VFT, ERP 和 VP 的上述变化, 0.1 mmol · L^{-1} 仅对抗 VFT 降低和 VP 延长, 且作用较弱. Cim 0.01 mmol · L^{-1} 则未见明显影响. 结果表明 Cim 对大鼠复灌心室肌电生理特性具浓度相关性保护作用.

关键词 心室纤颤; 电生理; 西咪替丁; 心肌再灌注损伤

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