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Early and delayed protection by capsaicin against reperfusion injury in rat hearts[1]

ZHOU Fu-Wen, LI Yuan-Jian[2], DENG Han-Wu
(*Department of Pharmacology, Hunan Medical University, Changsha 410078, China*)

KEY WORDS capsaicin; myocardial reperfusion injury; calcitonin gene-related peptide; heart function tests

ABSTRACT

AIM: To study early or delayed cardioprotection afforded by pretreatment with capsaicin. **METHODS**: The isolated rat heart was perfused in a Langendorff model. Heart rate, coronary flow, left ventricular pressure, and its first derivative ($\pm dp/dt_{max}$) were recorded, and the calcitonin gene-related peptide-like immunoreactivity (CGRP-LI) and the release of creatine kinase (CK) were measured. **RESULTS**: Capsaicin (50 $mg \cdot kg^{-1}$, sc) improved the recovery of cardiac function and decreased the release of CK. CK was (2.12 ± 0.40) and (0.26 ± 0.04) $u \cdot min^{-1} \cdot g^{-1}$ (wet wt) for ischemia-reperfusion (I/R) and capsaicin + I/R, respectively ($P < 0.05$). Capsaicin treatment caused an increase in the concentration of CGRP-LI in plasma. CGRP-LI was (135 ± 12) and (304 ± 45) $ng \cdot L^{-1}$ for vehicle + I/R and capsaicin + I/R, respectively ($P < 0.05$). After pretreatment with capsaicin to deplete the sensory nerve transmitter content, the cardioprotection and the increased level of CGRP by capsaicin were abolished. A delayed protection was shown in the hearts obtained from the rats pretreated with capsaicin 24 h or 48 h before the experiments. **CONCLUSION**: Pretreatment with capsaicin induces the early and delayed cardioprotection, which may be related to stimulation of CGRP release in the rat.

INTRODUCTION

Preconditioning stimulus, such as transient ischemia not only triggers short-lasting early preconditioning, but also induces delayed or second window cardioprotection[1]. The mechanism responsible for the early and delayed cardioprotection of preconditioning is not fully understood. Experimental evidence suggested that the neurogenic machanism might be involved in ischemic cardioprotection, and peptidergic and sympathetic nerves participate in the mediation of ischemic preconditioning[2,3]. Exogenous administration of α-adrenoceptor agonists or drugs which stimulate the release of transmitters from sympathetic nerves can substitute for preconditioning ischemia[3-5].

Capsaicin-sensitive sensory nerves are widely distributed in cardiovascular tissues, and calcitonin gene-related peptide (CGRP), a principal transmitter in capsaicin-sensitive sensory nerves[6], protects the myocardium against injury due to ischemia-reperfusion[2]. Recently, we and others have shown that CGRP participates in the mediation of the early protection of ischemic preconditioning in the rat isolated heart[2,7-9]. Capsaicin selectively stimulates the release of sensory nerve transmitters including CGRP[10]. There is evidence to suggest that in the isolated rat heart, pretreatment with capsaicin protected against myocardial injury induced by ischemia-reperfusion[8,9]. Therefore, the present study examined whether pretreatment with capsaicin induced delayed protection in the rat heart.

MATERIALS AND METHODS

Reagents Capsaicin, purchased from Sigma, was dissolved in a vehicle containing ethanol 10 %,

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[2] Correspondence to Prof LI Yuan-Jian.
Phn 86-731-447-4411, ext 2704. Fax 86-731-447-1339.
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Tween-80 10 %, and saline 80 %. Radioimmunoassay kits for measurement of CGRP were obtained from Dongya Immunity Technology Institution. Creatine kinase (CK) assay kits were obtained from Baoding Chemical Company.

Preparation of the isolated heart Sprague-Dowley rats (♂, $n = 42$, $220 \pm s$ 20 g) were supplied by the Experimental Animal Center of Hunan Medical University (Grade Ⅱ, No 20011). Rats were anesthetized with sodium pentobarbital (45 $mg \cdot kg^{-1}$, ip). The heart was rapidly excised, mounted, and perfused on a modified Langendorff apparatus at a constant pressure of 8 kPa. The heart was perfused with Krebs-Henseleit (K-H) buffer (37 ℃, pH 7.4), saturated with 95 % O_2 + 5 % CO_2. The K-H buffer had the following composition: NaCl 119.0, $NaHCO_3$ 25.5, KCl 4.3, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, and glucose 11.0 $mmol \cdot L^{-1}$.

A water-filled latex balloon was inserted into the left ventricle through the left atrium[11]. The heart rate (HR), left ventricular pressure (LVP), and its first derivative ($\pm dp/dt_{max}$) were continuously monitored. The resulting electric signals were digitized by MacLab analogue to digital converter and recorded by Power Macintosh 7220 computer. Coronary flow (CF) was measured by timed collection and the sample of coronary effluent at 5 min of reperfusion was collected for measurement of creatine kinase.

Determination of plasma CGRP concentration Blood samples (3 mL) were collected from the carotic artery in tubes (containing 10 % edetic acid 40 μL and aprotinin 400 $mU \cdot L^{-1}$), and centrifuged at 1300 × g at 4 ℃ for 10 min. The plasma was collected and stored at − 20 ℃ until assay. CGRP-like immunoreactivity (CGRP-LI) was measured by RIA kits.

Creatine kinase assay Myocardial injury was monitored by assaying the release of CK from the isolated heart. The CK activity in the coronary effluent at 5 min of reperfusion was measured spectrophotometrically.

Experimental protocols Hearts were equilibrated for 15 min before the experiments. In the control group, the heart was perfused with K-H buffer solution throughout the experiment. In the ischemia-reperfusion group, the heart was subjected to a 30-min stopping perfusion followed by a 30-min reperfusion. In the case of capsaicin, rats were treated with a single dose capsaicin (50 $mg \cdot kg^{-1}$) for 30 min, 24 h, or 48 h before the experiments for early or delayed protection, respectively. Capsaicin was administered by sc injection under pentobarbital anesthesia. To confirm the depletion of transmitter content in sensory nerves and to rule out a direct effect of capsaicin on the myocardium, after capsaicin treatment for 4 d, the rats were again injected with capsaicin (50 $mg \cdot kg^{-1}$) 30 min prior to the experiments. In the vehicle-treated group, the rat was treated with vehicle alone.

Statistics Data were expressed as $\bar{x} \pm s$ and analyzed with one-way ANOVA. When the significance was indicated between groups, a Tukey's test was performed[12].

RESULTS

Early protection of capsaicin In the control group, continuously perfused rat hearts were observed for 90 min. There were no changes in CF, LVP, $\pm dp/dt_{max}$, and HR. The 30-min stoppage perfusion and the 30-min reperfusion caused a decrease in heart function and an increase in the release of CK. Acute application improved the recovery of heart function and reduced the release of CK. However, after pretreatment with capsaicin to deplete sensory nerve transmitter content, the heart dysfunction and the increased release of CK elicited by ischemia reperfusion were not affected by capsaicin at the second injection (Tab 1, 2).

CGRP-LI concentration in plasma CGRP-LI concentration in plasma of the rats treated with capsaicin 30 min before the experiment was increased compared with that of control rats. However, after pretreatment with capsaicin to deplete sensory transmitter 4 d before the experiments, the elevated level of CGRP-LI by acute application of capsaicin also disappeared (Tab 3).

Delayed protection of capsaicin As shown in Tab 1, the recovery of HR, CF, LVP, $\pm dp/dt_{max}$ was improved in the rats pretreated with capsaicin 24 or 48 h before the experiments. Pretreatment with capsaicin 24 or 48 h before the experiments also declined the release of CK (Tab 2).

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E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

Tab 1. Effect of capsaicin on hemodynamic changes elicited by ischemia reperfusion. Cap (30 min), Cap (24 h) or Cap (48 h): capsaicin treatment 30 min, 24 h, or 48 h before the experiments respectively. Cap (4 d) & Cap (30 min): capsaicin treatment 30 min before the experiments in the rats pretreated with capsaicin for 4 d. $\bar{x} \pm s$. $n = 6$ rats. $^cP < 0.01$ *vs* control. $^dP > 0.05$ *vs* I/R. $^iP < 0.01$ *vs* vehicle. $^jP < 0.01$ *vs* Cap (30 min).

	Pre-ischemia	Reperfusion/min 5	10	20	30
Left ventricular pressure/kPa					
Control	10.3 ± 0.5	10.3 ± 0.7	10.3 ± 0.5	10.3 ± 0.5	10.1 ± 0.7
Ischemia/reperfusion	10.8 ± 1.5	2.9 ± 0.3^c	3.3 ± 0.4^c	3.7 ± 0.5^c	4.1 ± 0.7^c
+ Vehicle	10.5 ± 1.1	2.9 ± 0.4^d	3.2 ± 0.4^d	3.7 ± 0.5^d	4.1 ± 0.5^d
+ Cap (30 min)	10.8 ± 0.8	8.3 ± 0.7^i	8.7 ± 0.8^i	9.2 ± 0.7^i	9.7 ± 0.5^i
+ Cap (4 d) & Cap (30 min)	10.8 ± 0.9	3.2 ± 0.4^j	3.5 ± 0.5^j	3.9 ± 0.5^j	4.1 ± 0.4^j
+ Cap (24 h)	10.5 ± 0.9	6.4 ± 0.8^i	6.9 ± 0.8^i	7.6 ± 0.8^i	8.4 ± 0.7^i
+ Cap (48 h)	10.5 ± 0.9	6.9 ± 0.5^i	7.5 ± 0.7^i	8.1 ± 0.8^i	9.1 ± 0.8^i
$+dp/dt_{max}$/kPa·s^{-1}					
Control	308 ± 33	305 ± 34	307 ± 34	304 ± 32	301 ± 32
Ischemia/reperfusion	321 ± 29	65 ± 6^c	76 ± 6^c	101 ± 8^c	137 ± 14^c
+ Vehicle	319 ± 19	64 ± 6^d	86 ± 10^d	93 ± 15^d	131 ± 14^d
+ Cap (30 min)	310 ± 27	217 ± 19^i	239 ± 19^i	259 ± 14^i	289 ± 20^i
+ Cap (4 d) & Cap (30 min)	308 ± 23	61 ± 5^j	76 ± 12^j	94 ± 13^j	123 ± 15^j
+ Cap (24 h)	320 ± 26	190 ± 15^i	214 ± 15^i	233 ± 20^i	256 ± 21^i
+ Cap (48 h)	323 ± 29	199 ± 20^i	222 ± 22^i	250 ± 20^i	276 ± 25^i
$-dp/dt_{max}$/kPa·s^{-1}					
Control	221 ± 15	218 ± 17	217 ± 16	217 ± 14	216 ± 14
Ischemia/reperfusion	259 ± 14	52 ± 3^c	77 ± 4^c	92 ± 5^c	110 ± 6^c
+ Vehicle	227 ± 13	52 ± 3^d	72 ± 8^d	88 ± 8^d	109 ± 10^d
+ Cap (30 min)	230 ± 12	154 ± 10^i	175 ± 9^i	190 ± 6^i	205 ± 10^i
+ Cap (4 d) & Cap (30 min)	229 ± 11	53 ± 4^j	73 ± 9^j	88 ± 9^j	108 ± 11^j
+ Cap (24 h)	223 ± 8	133 ± 4^i	150 ± 12^i	167 ± 11^i	176 ± 9^i
+ Cap (48 h)	219 ± 12	143 ± 8^i	151 ± 9^i	169 ± 9^i	186 ± 10^i
Coronary flow/mL·min^{-1}					
Control	9.8 ± 0.9	9.7 ± 0.9	9.6 ± 0.7	9.6 ± 0.8	9.4 ± 0.7
Ischemia/reperfusion	9.7 ± 1.0	4.2 ± 0.6^c	4.3 ± 0.8^c	4.3 ± 0.6^c	4.3 ± 0.5^c
+ Vehicle	9.6 ± 1.3	3.8 ± 0.8^d	4.1 ± 0.8^d	4.2 ± 0.7^d	4.4 ± 0.7^d
+ Cap (30 min)	9.6 ± 1.0	8.2 ± 0.5^i	8.2 ± 0.6^i	8.3 ± 0.4^i	8.6 ± 0.6^i
+ Cap (4 d) & Cap (30 min)	9.7 ± 1.1	4.3 ± 0.3^j	4.3 ± 0.2^j	4.5 ± 0.3^j	4.5 ± 0.4^j
+ Cap (24 h)	10.0 ± 1.3	7.4 ± 1.0^i	7.7 ± 1.1^i	7.9 ± 1.0^i	8.1 ± 1.1^i
+ Cap (48 h)	9.9 ± 1.2	8.2 ± 0.7^i	8.3 ± 0.7^i	8.7 ± 0.7^i	8.8 ± 0.7^i
Heart rate/beats·min^{-1}					
Control	317 ± 17	309 ± 16	308 ± 16	308 ± 16	308 ± 17
Ischemia/reperfusion	310 ± 17	148 ± 11^c	160 ± 13^c	179 ± 11^c	208 ± 15^c
+ Veh (30 min)	312 ± 15	143 ± 7^d	167 ± 9^d	186 ± 9^d	207 ± 18^d
+ Cap (30 min)	309 ± 15	285 ± 15^i	269 ± 16^i	279 ± 17^i	292 ± 18^i
+ Cap (4 d) & Cap (30 min)	308 ± 17	141 ± 13^j	166 ± 10^j	180 ± 17^j	215 ± 22^j
+ Cap (24 h)	315 ± 14	240 ± 11^i	252 ± 9^i	260 ± 11^i	270 ± 11^i
+ Cap (48 h)	311 ± 17	253 ± 9^i	262 ± 8^i	269 ± 9^i	282 ± 12^i

DISCUSSION

It had been suggested that the neurogenic mechanism was involved in the cardioprotection of ischemic preconditioning, and capsaicin-sensitive sensory nerves participated in the mediation of ischemic

Tab 2. Effects of capsaicin on CK release in coronary effluent. Cap (30 min), Cap (24 h) or Cap (48 h): capsaicin treatment 30 min, 24 h or 48 h before the experiments respectively. Cap (4 d) & Cap (30 min): capsaicin treatment 30 min before the experiments in the rats pretreated with capsaicin for 4 d.
[c] $P<0.01$ *vs* control. [d] $P>0.05$ *vs* I/R.
[i] $P<0.01$ *vs* vehicle. [j] $P<0.01$ *vs* Cap (30 min).

	Rats	CK/u·min^{-1}·g^{-1} (wet wt)
Control	6	0.20 ± 0.02
Ischemia/reperfusion	6	2.12 ± 0.40[c]
+ Vehicle	6	2.13 ± 0.41[d]
+ Cap (30 min)	6	0.26 ± 0.04[i]
+ Cap (4 d) & Cap (30 min)	6	2.12 ± 0.42[j]
+ Cap (24 h)	6	0.34 ± 0.04[i]
+ Cap (48 h)	6	0.28 ± 0.04[i]

Tab 3. Effect of capsaicin on plasma CGRP-LI level. Cap (30 min), Cap (24 h) or Cap (48 h): capsaicin treatment 30 min, 24 h, or 48 h before the experiments respectively. Cap (4 d) & Cap (30 min): capsaicin treatment 30 min before the experiments in the rats pretreated with capsaicin for 4 d. [a] $P>0.05$ *vs* control.
[d] $P>0.05$, [e] $P<0.05$, [f] $P<0.01$ *vs* vehicle.
[i] $P<0.01$ *vs* Cap (30 min).

	Rats	CGRP/ng·L^{-1}
Control	7	137 ± 10
+ Vehicle	6	135 ± 12[a]
+ Cap (30 min)	7	304 ± 45[f]
+ Cap (4 d) & Cap (30 min)	6	99 ± 6[i]
+ Cap (24 h)	6	129 ± 11[d]
+ Cap (48 h)	6	110 ± 12[e]

preconditioning. The protective effects of ischemic preconditioning were abolished by CGRP8-37, a selective receptor antagonist[7], and pretreatment with CGRP or capsaicin produced preconditioning-like protection in the isolated perfused rat heart[2,8]. The protective effects of pacing-induced preconditioning was negated by pretreatment with capsaicin to deplete sensory nerve transmitter content[13]. More recently, it has been found that pretreatment with capsaicin aggravates myocardial infarction in the porcine heart[14]. In the present study, acute application of capsaicin enhanced the plasma level of CGRP concomitantly with an improvement of the recovery of heart function. To confirm the protection of CGRP-mediated preconditioning, capsaicin was used. It has been demonstrated that capsaicin depletes selectively sensory nerve transmitters including CGRP. In the guinea pig or the rat, pretreatment with capsaicin (total dose 50 mg/kg, sc) two wk prior to the experiments caused an almost total loss of SP- and CGRP-immunoreactive nerves within the heart[13]. Recently, others have shown that pretreatment with capsaicin 3 d prior to the experiments abolishes the protective effects of pacing-induced preconditioning in the rat. In the hearts obtained from capsaicin-treated animals, immunoreactive fibers are scarce in the atria and CGRP release detected from coronary effluents is completely eliminated[15]. In the present study, pretreatment with capsaicin 4 d before the experiments abrogated the cardioprotection and the increased release of CGRP by capsaicin. These findings suggest that activation of sensory nerves by ischemia or capsaicin has beneficial effects of myocardial injury due to ischemia-reperfusion.

A major new finding of this study was that pretreatment with capsaicin induced a delayed protection against ischemia-reperfusion injury. Studies in the literature suggest that the delayed protection of ischemic or pharmacological preconditioning is also related to the release of endogenous cardiovascular active substances. Recently, we showed that delayed protection by brief remote organ ischemia were attenuated by pretreatment with capsaicin[16], in further support the hypothesis that CGRP may play an important role in the delayed protection.

It is well known that CGRP, substance P and neurokinin A co-exist in capsaicin-sensitive sensory nerves, and capsaicin selectively evokes the release of them[10]. Endogenous or exogenous CGRP has been shown to protect the myocardium and endothelial cells[17-20]. Although direct cardioprotection of substance P or neurokinin A has not yet been reported, a contribution by them cannot be completely ruled out. Therefore, further studies regarding the mechanisms for the protection are warranted.

In conclusion, the present study suggests that pretreatment with capsaicin induces the early and delayed cardioprotection, and that protective effects of capsaicin may be related to stimulation of CGRP release in the rat.

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辣椒辣素对大鼠再灌注损伤的心肌早期和延迟保护作用[1]

周伏文，李元建[2]，邓汉武
（湖南医科大学药理教研室，长沙 410078，中国）

关键词 辣椒辣素；心肌再灌注损伤；降钙素基因相关肽；心脏功能实验

目的：研究辣椒辣素预处理的早期和延迟心肌保护．**方法**：采用 Langendorff 装置灌注离体心脏．记录心率、冠脉流量、左室内压以及最大变化速率，并测定降钙素基因相关肽(CGRP)的血浆浓度及灌注液中肌酸激酶(CK)的释放量．**结果**：辣椒辣素(50 mg·kg^{-1}，sc)改善心功能、降低 CK 释放，并升高 CGRP 的血浆浓度．预先用辣椒辣素耗竭感觉神经递质后，辣椒辣素的心肌保护和升高 CGRP 血浆浓度作用消失．应用辣椒辣素 24 h 或 48 h 后，其对缺血心肌仍具有保护作用．**结论**：辣椒辣素能诱导早期和延迟心肌保护，其保护作用可能与促进 CGRP 释放有关．

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