TRPV1 Gene Knockout Impairs Postischemic Recovery in Isolated Perfused Heart in Mice

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Background—Although pharmacological studies suggest that the transient receptor potential vanilloid type 1 (TRPV1) channels expressed in sensory nerve fibers innervating the heart may exert a cardioprotective effect, definitive evidence supporting such a notion is lacking. In addition, function and regulation of sensory neuropeptides, namely, calcitonin gene–related peptide (CGRP) and substance P (SP), in the face of challenges induced by cardiac injury in the presence or absence of the TRPV1 are largely unknown.

Methods and Results—The hearts of gene-targeted TRPV1-null mutant (TRPV1−/−) mice or wild-type (WT) mice were perfused in a Langendorff apparatus in the presence or absence of capsazepine (a TRPV1 receptor antagonist), CGRP, CGRPΔ(8–37) (a CGRP receptor antagonist), SP, or RP67580 (a neurokinin-1 [NK1] receptor antagonist) when hearts were subjected to 40 minutes of ischemia and 30 minutes of reperfusion. Hemodynamic alterations and SP release measured by radioimmunoassay were assessed before and after ischemia/reperfusion injury of the heart. Expression of the NK1 receptor in the hearts of TRPV1−/− and WT mice were determined with the use of Western blot analyses. Impairment of postischemic recovery, defined by increased left ventricular end-diastolic pressure (LVEDP) and decreased left ventricular developed pressure (LVDP) and coronary flow (CF), was more severe in TRPV1−/− hearts than in WT hearts. Although it had no effect on postischemic recovery of TRPV1−/− hearts, blockade of the TRPV1 with capsazepine caused a most severe impairment of postischemic recovery in WT hearts compared with untreated WT and TRPV1−/− hearts. Exogenous CGRP and SP produced a significant improvement in postischemic recovery in both TRPV1−/− and WT hearts, and the maximal functional improvement in TRPV1−/− hearts was not different from that of WT hearts except that SP-induced increases in LVEDP were larger in the former than in the latter. Blockade of the NK1 receptor with RP67580, but not blockade of the CGRP receptor with CGRPΔ(8–37), caused more severe impairment in postischemic recovery in both TRPV1−/− and WT hearts than in untreated hearts in both genotypes. The release of SP after ischemia/reperfusion injury was increased in both WT and TRPV1−/− hearts, albeit with a smaller magnitude of the increase in the latter. Capsazepine attenuated injury-induced SP release in WT but not TRPV1−/− hearts. There was no difference in the expression of the NK1 receptor between the 2 genotype hearts.

Conclusions—Thus, our data show that (1) TRPV1 gene deletion decreases injury-induced SP release and impairs cardiac recovery function after ischemia/reperfusion injury; (2) TRPV1 gene deletion leads to reconditioning of the heart with improved postischemic recovery compared with that induced by acute TRPV1 blockade and in terms of cardiac response to exogenous SP; and (3) blockade of the NK1 but not CGRP receptors worsens postischemic recovery of hearts in both genotypes. Taken together, these data indicate that TRPV1 plays a role in protecting the heart from injury possibly via increasing SP release and that deletion of this receptor reconditions the heart for escaping, at least in part, from injury possibly via enhancing NK1 receptor function. (Circulation. 2005;112:3617-3623.)

Key Words: heart disease ■ myocardial infarction ■ reperfusion ■ nervous system ■ TRPV1 protein, mouse

Capsaicin-sensitive sensory nerves are widely distributed in the cardiovascular system, including the heart, kidney, and blood vessels.1,2 These nerves can be activated by a variety of physical and chemical stimuli that present challenges to homeostasis and can be characterized by their sensitivity to capsaicin,3,4 a compound that activates the transient receptor potential vanilloid type 1 (TRPV1) channels.5 TRPV1 is a nonselective cation channel that, when activated by capsaicin, noxious heat, and protons,6–7 causes the release of neurotransmitters including substance P (SP) and calcitonin gene–related peptide (CGRP) from peripheral nerve terminals, leading to cardiovascular responses.8,9
The TRPV1 channels have recently been found to be distributed on the epicardial surface of the ventricle, and the importance of this channel in the regulation of heart function has recently been highlighted. The TRPV1 expressed in the cardiac sensory nerves may function as a molecular sensor to detect tissue ischemia and may modulate cardiac function directly or via activating other cardiac nociceptors. Pharmacological studies indicate that activation of the TRPV1 with exogenous agonists plays a significant cardioprotective role after myocardial ischemia/reperfusion injury. In these studies, however, myocardial ischemia itself may also activate the TRPV1 given that tissue pH decreases as CO2 and protons accumulate during this process. Moreover, ischemic conditions in the heart and brain increase the levels of endovanilloids including anandamide, lipoxigenase products of arachidonic acid, and N-acylethanolamines, all of which may activate the TRPV1 channels directly or indirectly. Thus, the use of pharmacological tools alone may not be sufficient in defining the role of the TRPV1.

Exogenous CGRP and SP have been suggested to protect against ischemic myocardial injury. Pretreatment of isolated hearts with a SP receptor antagonist impairs postischemic recovery, suggesting a role for endogenously released SP in cardioprotection. In noncardiac tissues, CGRP appears to be the key neurotransmitter released from sensory terminals to dilate mesenteric arteries in rats. In contrast, increased renal pelvic pressure results in an increase in afferent renal nerve activity that can be blocked by a SP but not CGRP receptor antagonist. Although it is known that activation of the TRPV1 may lead to the release of CGRP and SP, the discharge and function of these neuropeptides in the face of ischemia/reperfusion injury in the absence of the TRPV1 are unknown.

In the present study we used combined genetic and pharmacological approaches to test the hypothesis that the TRPV1 expressed in sensory nerves innervating the heart plays a role in protecting against myocardial injury and the lack or blockade of the TRPV1 impairs postischemic recovery. To accomplish this, we performed ischemia/reperfusion studies of isolated perfused hearts using a mouse model in which the TRPV1 gene (gene locus symbol 11B3) was disrupted. These studies were performed in the absence and presence of a selective TRPV1 receptor antagonist to assess the possibility that there are compensatory changes after a long-term absence of the TRPV1. We also investigated the cardioprotective effects in the presence of exogenous CGRP and SP or their selective receptor antagonists. Our data provide direct evidence that the loss of the TRPV1 impairs postischemic recovery and indicate the possible mechanisms.

**Methods**

**Langendorff Heart Preparation and Measurements of Cardiac Function**

Male TRPV1 gene knockout (TRPV1−/−) strain B6.129S4-TRPV1−/− and control wild-type (WT) strain C57BL/6J mice were used (Jackson Laboratory, Bar Harbor, Maine). Mice were heparinized (500 U/kg IP) and anesthetized with urethane (780 mg/kg IP). Hearts from TRPV1−/− and WT mice were cannulated and retrogradely perfused at 37°C and 80 mm Hg with Krebs-Henseleit buffer (118 mmol/L NaCl, 4.7 mmol/L KCl, 1.2 mmol/L MgSO4, 1.2 mmol/L KH2PO4, 2.5 mmol/L CaCl2, 25 mmol/L NaHCO3, 0.5 mmol/L Na-EDTA, and 11 mmol/L glucose, saturated with 95% O2/5% CO2, pH 7.4) through the aorta in a noncirculating Langendorff apparatus, as described previously. A water-filled balloon was inserted into the left ventricle and adjusted to a left ventricular end-diastolic pressure (LVEDP) of 5 to 8 mm Hg. The distal end of the catheter was connected to a Digi-Med Heart Performance Analyzer via a pressure transducer, and coronary flow (CF) was measured by a flowmeter with an online probe.

Hearts were paced at 350 bpm except during ischemia, and pacing was reinitiated 2 minutes after reperfusion. After a 25-minute equilibration period, hearts were subjected to 40 minutes of no-flow normothermic global ischemia, followed by 30 minutes of reperfusion. The LVEDP, left ventricular developed pressure (LVPD) (peak systolic minus end-diastolic left ventricular pressure), and CF were measured during the process. The experiments were approved by the Michigan State University Animal Care and Use Committee.

**Experimental Protocols**

Five experimental series were conducted, as follows.

**Experiment 1: Perfusion With Capsazepine**

These experiments were performed to determine the function of the TRPV1 receptor during ischemia/reperfusion injury and the difference of cardiac functions between long-term and short-term absence of the TRPV1 receptor. As normal controls (nonischemic), WT and TRPV1−/− hearts were perfused for 95 minutes. In experiments performed in the absence of the TRPV1 receptor antagonist, hearts from WT and TRPV1−/− mice were subjected to ischemia and reperfusion as described above, and cardiac function was measured. For acute blockade of the TRPV1 receptor, hearts from WT and TRPV1−/− mice were perfused with Krebs-Henseleit buffer for a 25-minute equilibration period, and capsazepine (10−6 mol/L), a selective antagonist of the TRPV1 receptor, was added to the perfusate 5 minutes before ischemia. Two additional concentrations of capsazepine, 10−5 and 10−7 mol/L, and another selective TRPV1 receptor antagonist, ruthenium red (10−5 mol/L), were used in WT hearts. WT hearts were also perfused with capsazepine (10−6 mol/L) for 95 minutes without ischemia/reperfusion injury as an additional control.

**Experiment 2: Perfusion With CGRP**

The effect of exogenous CGRP on cardiac function during ischemia and reperfusion was assessed. Hearts from WT and TRPV1−/− mice were subjected to a 25-minute equilibration period and perfused with CGRP (10−6 mol/L) added to the perfusate 5 minutes before ischemia. Additional WT hearts were perfused with CGRP (10−7 mol/L) to confirm the specificity of the CGRP effect.

**Experiment 3: Perfusion With CGRP Physiological**

To determine the role of endogenous CGRP during ischemia and reperfusion in both WT and TRPV1−/− hearts, CGRP (10−5 mol/L) was added to the perfusate alone. Hearts from WT and TRPV1−/− mice were perfused with CGRP (10−6 mol/L) added to the perfusate 5 minutes before ischemia. Two additional concentrations of CGRP (10−6 mol/L and 10−7 mol/L) were also used in WT hearts. WT hearts were also perfused with capsazepine (10−6 mol/L) for 95 minutes without ischemia/reperfusion injury as a control.

**Experiment 4: Perfusion With SP**

Hearts from WT and TRPV1−/− mice were subjected to a 25-minute equilibration period and perfused with SP (10−6 mol/L) added to the perfusate 5 minutes before ischemia. Additional WT hearts were perfused with RP67580 (a selective neurokinin-1 [NK1] receptor antagonist; 10−6 mol/L) added to the perfusate 5 minutes before the addition of SP (10−6 mol/L) to confirm the specificity of the SP effect.

**Experiment 5: Perfusion With RP67580**

Hearts from WT and TRPV1−/− mice were subjected to a 25-minute equilibration period and perfused with RP67580 (10−6 mol/L) added
to the perfusate 5 minutes before ischemia. Two additional concentrations of RP67580, 10^{-3} mol/L and 10^{-2} mol/L, were used in WT hearts. WT hearts were perfused with RP67580 (10^{-5} mol/L) for 95 minutes without ischemia/reperfusion injury as a control.

Measurement of SP

The WT and TRPV1^{-/-} hearts were cut into pieces and put into the tube containing 1.5 mL Krebs-Henseleit buffer that was saturated with 95% O2/5% CO2 continuously for 70 minutes (normal control group) as described.27 In experimental groups, the WT and TRPV1^{-/-} hearts were saturated with 95% O2/5% CO2 for 30 minutes after 40 minutes of incubation without O2 (the ischemia/reperfusion group). Additional WT and TRPV1^{-/-} hearts were treated the same as in the ischemia/reperfusion group except that capsazepine (10^{-2} mol/L) was added to the solution. The samples were purified and analyzed by radioimmunoassay (SP rat RIA kits; Peninsula Laboratories) as described previously for determination of SP release, which was normalized by the heart weight.28

Western Blot of the NK1 Receptor

Membrane protein of the whole heart was extracted. Immunoblotting and protein quantification were performed as described before.29 Blots were incubated with the rabbit polyclonal anti-NK1 receptor (Abcam Inc, 1:1000) and monoclonal anti-β-actin (Sigma, 1:2000).

Statistical Analysis

All values are expressed as mean±SEM. The groups of WT hearts subjected to ischemia/reperfusion injury and TRPV1^{-/-} hearts subjected to ischemia/reperfusion injury represent the same animals in Figures 1 to 5. Differences among groups with multiple measurements over time were determined by ANOVA (2-way ANOVA) for repeated measurements, and differences between means were identified by the least significant difference test (symbols in the time course plots of each figure in the online-only Data Supplement; see http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.556274/DC1). Comparisons among groups measured at the end of the ischemia/reperfusion experiments in the bar charts of each figure and in SP release experiments were performed by 1-way ANOVA analysis followed by the Tukey-Kramer multiple comparison test. The difference in NK1 receptor expression between WT and TRPV1^{-/-} hearts was determined by the Student t test. The results were considered statistically significant at P<0.05.

Results

Postischemic Recovery Is Impaired in TRPV1^{-/-} Hearts

There was no significant difference in LVEDP, LVDP, and CF between WT and TRPV1^{-/-} hearts in control nonischemic groups (online-only Data Supplement Figure I). After ischemia and during reperfusion, WT hearts exhibited a better recovery compared with TRPV1^{-/-} hearts with lower LVEDP and higher LVDP and CF (Figure 1).

Acute Blockade of the TRPV1 Receptor Causes More Severe Impairment of Postischemic Recovery in WT Hearts

Blockade of the TRPV1 receptor with capsazepine (10^{-6} mol/L) increased LVEDP and decreased LVDP and CF during reperfusion after ischemic injury in WT hearts (Figure 1). The impairments in these parameters were more profound in WT hearts perfused with capsazepine than in TRPV1^{-/-} hearts with or without capsazepine perfusion. Capsazepine at higher (10^{-3} mol/L) or lower (10^{-2} mol/L) concentrations also impaired the postischemic recovery in WT hearts. Although the higher concentration of capsazepine tended to impair cardiac function more severely, there was no statistically significant difference (data not shown). Capsazepine alone had no effect on cardiac function in WT hearts without ischemia (online-only Data Supplement Figure I). Another TRPV1 receptor antagonist, ruthenium red (10^{-6} mol/L),
impaired the postischemic recovery in WT hearts in a manner similar to that of capsazepine (data not shown).

**Exogenous CGRP Improves Postischemic Recovery**

Perfusion of exogenous CGRP (10^{-7} mol/L) improved postischemic recovery by decreasing LVEDP and increasing LVDP and CF to the same extent in WT and TRPV1^{-/-} hearts (Figure 2). The beneficial effects of CGRP on lowering LVEDP and increasing LVDP and CF were abolished when the hearts were pretreated with CGRP_{8-37} (10^{-6} mol/L) (online-only Data Supplement Figure II), indicating that these effects are specifically mediated by activation of the CGRP receptor.

**Blockade of the CGRP Receptor Had No Effect on Postischemic Recovery**

CGRP_{8-37}, at a concentration (10^{-6} mol/L) shown to block the cardioprotective effect of exogenous CGRP (online-only Data Supplement Figure II), had no effect on postischemic recovery in the hearts from both WT and TRPV1^{-/-} mice (Figure 3). Likewise, higher (10^{-5} mol/L) or lower (10^{-7} mol/L) concentrations of CGRP_{8-37} had no effect on postischemic recovery in WT hearts (data not shown). In addition, CGRP_{8-37} (10^{-6} mol/L) had no effect on cardiac function in WT hearts without ischemia (online-only Data Supplement Figure III). These data indicated that endogenous CGRP may not be responsible for the cardioprotective effect induced by TRPV1 activation.

**Exogenous SP Improves Postischemic Recovery**

SP (10^{-6} mol/L) decreased LVEDP and increased LVDP and CF in both WT and TRPV1^{-/-} hearts (Figure 4). The protective effects of SP were abolished in the presence of the NK1 receptor antagonist RP67580 (10^{-6} mol/L) (online-only Data Supplement Figure IV), indicating specificity. The increase in LVDP induced by SP was significantly larger in TRPV1^{-/-} hearts than in WT hearts, indicating that compensatory mechanisms may be developed in TRPV1^{-/-} hearts to protect the heart from injury.

**Blockade of the SP Receptor Impairs Postischemic Recovery**

Postischemic recovery of LVEDP and LVDP was impaired in both WT hearts and TRPV1^{-/-} hearts when the NK1 receptor was blocked by RP67580 (10^{-6} mol/L) (Figure 5), indicating that endogenous SP plays a role in cardioprotection after injury. Moreover, RP67580 impaired CF during reperfusion in WT but not TRPV1^{-/-} hearts (Figure 5). RP67580 (10^{-6} mol/L) had no effect on cardiac function in WT hearts without ischemia (online-only Data Supplement Figure V). Higher (10^{-5} mol/L) or lower (10^{-7} mol/L) doses of RP67580 had the same effect as that evoked by RP67580 at 10^{-6} mol/L.

**Release of SP in Experimental Groups**

The release of SP at baseline (normal control) was not different between WT and TRPV1^{-/-} hearts. SP release in WT and TRPV1^{-/-} hearts subjected to ischemia/reperfusion increased remarkably compared with the baseline (P<0.01), but the magnitude of the increase was smaller in TRPV1^{-/-} hearts than in WT hearts (P<0.05). Furthermore, blockade of the TRPV1 receptor with capsazepine attenuated SP release in WT but not TRPV1^{-/-} hearts subjected to ischemia/reperfusion treatment, indicating that SP release in WT hearts is partially mediated by the TRPV1 receptor (Figure 6).
Expression of the NK1 Receptor in WT and TRPV1−/− Hearts

Western blot was performed to examine the NK1 receptor content in WT and TRPV1−/− hearts. There was no significant difference in the expression of the NK1 receptor in the WT (0.75±0.07; n=4) and TRPV1−/− hearts (0.88±0.05; n=4) (P>0.05).

Discussion

Although a wealth of pharmacological data indicates that activation of the TRPV1 receptor by its agonists exerts a cardioprotective effect,12–14 definitive evidence generated by the use of alternative experimental approaches without ambiguity of nonspecific binding of the compounds is lacking. The objective of this study was to use genetically modified mice carrying a null mutation in the TRPV1 receptor gene to determine the function of the TRPV1 receptor on cardioprotection against myocardial ischemia/reperfusion injury. We and others have previously shown that chronic afferent denervation induced by neonatal capsaicin treatment results in sensory nerve degeneration, which entails not only down-regulation of the TRPV1 receptors but also depletion of sensory neuropeptides including CGRP and SP.2,5,9,13,21,27,28

Thus, for any given changes resulting from capsaicin treatment, it is unknown whether the changes are caused by reduced release of sensory neuropeptides or decreased expression of the TRPV1 channels. In fact, sensory nerve degeneration induced by capsaicin is a quite nonspecific change that involves loss of an array of receptors, channels, and neuropeptides expressed in these nerves.

In contrast, the TRPV1−/− mouse affords a model in which targeted ablation of the TRPV1 channel occurs. The fact that basal SP release is similar in the WT and TRPV1−/− hearts indicates that, in distinction from that of capsaicin-treated rats, sensory neuropeptide synthesis and release in TRPV1−/− mice are not impaired under the resting condition. Although it is unknown whether TRPV1 receptor expression is altered after cardiac ischemia in humans, the TRPV1−/− mouse model provides a unique tool for studying the potential TRPV1 action during ischemia/reperfusion injury by comparing the function of hearts containing or lacking the TRPV1 channels.

Our data show that genetic ablation of the TRPV1 receptor impairs the myocardial recovery during reperfusion after acute ischemia. Given that posts ischemic recovery in response to exogenous CGRP and SP was improved to the same extent in WT and TRPV1−/− hearts, it is unlikely that TRPV1 gene deletion caused impairment in cardiomyocyte contractility. These results provide the first direct evidence indicating that the TRPV1 receptor plays an important role in cardioprotection during myocardial ischemia/reperfusion injury via a pathway that is independent of cardiomyocyte contractility.

Interestingly, acute pharmacological blockade of the TRPV1 receptor in WT hearts caused more severe impairment of posts ischemic recovery than that of the TRPV1−/− hearts. These results suggest that the long-term absence of the TRPV1 elicits compensatory changes that may partly negate the effects of blocking its activity over the short term. Several lines of evidence from the present study may explain the possible compensatory mechanisms. Although the endogenous SP release during ischemia and reperfusion in TRPV1−/− hearts was lower than that of WT hearts, it was higher than that of WT hearts when the TRPV1 receptor was blocked, indicating that the non–TRPV1–dependent mechanism of SP release during ischemia/reperfusion injury is enhanced in TRPV1−/− hearts. Given that the SP release was not directly measured from the perfusate because of technical difficulties and that the small number of samples per group was used because of the limited supply of TRPV1−/− mice, however, the precise relationship of TRPV1 and SP release needs to be confirmed when more sophisticated
analytical methods are developed. Furthermore, exogenous SP caused a better postischemic recovery in terms of increasing LVDP in TRPV1−/− hearts compared with WT hearts, indicating that SP receptor function was enhanced without increasing the receptor density in TRPV1−/− hearts. It has been shown that the cardioprotective effect of SP is mediated by the NK1 receptor,30,31 a neurokinin receptor subtype possessing a high affinity for SP.22

It is known that TRPV1 activation leads to release of neuropeptides such as SP, CGRP, and other neurokinins from sensory nerve terminals.8,9,33 Among these sensory neuropeptides, CGRP exerts marked cardiostimulatory and coronary vasodilatory effects in pig and guinea pig hearts,9,33 whereas SP appears to cause primarily coronary vasodilatation.9,34 Our findings that exogenous CGRP and SP improve recovery after ischemia/reperfusion injury in WT and TRPV1−/− hearts are in agreement with the previous reports.19–21 Furthermore, the fact that ischemia-induced SP release in WT hearts is attenuated by pharmacological blockade of the TRPV1 suggests that TRPV1 activation is responsible at least in part, for ischemia-induced SP release, although non–TRPV1-dependent SP release also exists. These findings are supported by previous studies showing that capsaicin-induced depletion of neuropeptides from primary sensory afferents impairs posts ischemic recovery in isolated rat hearts.21 These results indicate that SP mediates the cardioprotective effect of the TRPV1 receptor after ischemia and reperfusion injury.

The mechanisms leading to non–TRPV1-induced SP release are unknown. However, recent studies showed that ischemia followed by reperfusion caused production of inflammatory cytokines in the heart including interleukin-6 and cardiotrophin-1, which inhibited the expression of neuropeptide Y but stimulated the expression and release of SP in cultured neurons.35 In addition, our previous studies showed that infusion of endothelin-1 led to an increase in sensory neuropeptide release via activation of the ETα receptor.27 All these potential pathways in addition to the TRPV1-mediated pathway may mediate the SP release during ischemia/reperfusion injury. Further studies will be required to address the precise mechanisms underlying non–TRPV1-induced SP release during this process.

Previous studies show that CGRP may be the main neurotransmitter in regulating mesenteric arterial dilation in rats,22,23 but increasing renal pelvic pressure results in an increase in afferent renal nerve activity that is blocked by a NK1 but not CGRP receptor antagonist,24 indicating that mechanisms mediating the sensory nerve function are dependent on the stimuli and tissues examined. We found that blockade of the NK1 but not CGRP receptor impaired the recovery after ischemia in both WT and TRPV1−/− hearts. Indeed, Kallner et al36 have shown that no cardioprotective effect of CGRP could be proven in myocardial ischemia and reperfusion in the pig. These results, in conjunction with the results of SP release in response to ischemia injury, suggest that endogenous SP in the mouse heart protects the heart against ischemia and reperfusion injury.

The mechanisms underlying the protective effect of SP on the myocardium are unknown. It has been shown that SP causes nitric oxide release, leading to vasodilatation of coronary arteries of various species.37,38 Our data show that SP substantially improved coronary flow during reperfusion in both WT and TRPV1−/− hearts, which may contribute to the improved function of LVEDP and LVDP. Interestingly, however, SP-induced recovery of LVDP but not CF was greater in the TRPV1−/− hearts than in the WT hearts. Additionally, blockade of the NK1 receptor impaired the recovery of LVEDP and LVDP but not CF in the TRPV1−/− hearts. Thus, these data suggest that the protective effects of SP may not depend solely on improved total perfusion of the heart. It is possible that TRPV1 gene deletion affects the regional myocardial flow, leading to impairment of the beneficial effect of SP without altering total flow.21

In summary, the experiments presented in this study provide direct evidence that the TRPV1 plays a role in cardioprotection during ischemia and reperfusion via increasing SP release. Furthermore, genetic ablation of the TRPV1 elicits compensatory changes related to enhancement of non–TRPV1-dependent SP release and NK1 receptor function to protect against ischemia/reperfusion injury. Our data may have important clinical implications given that sensory nerve function is impaired under certain pathophysiological conditions such as diabetic and aging hearts39,40 in which the cardioprotective mechanisms against ischemia injury are impaired.41,42

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Disclosures
None.

References


19. Li YJ, Xiao ZS, Peng CF, Deng HW. Calcitonin gene-related peptide from peripheral nerve terminals, leading to altered cardiovascular responses. The experiments presented in this study, which used isolated perfused hearts from gene-targeted TRPV1-null mutant and wild-type mice in a Langendorff perfusion apparatus, provide direct evidence for the first time that TRPV1 plays an important role in cardioprotection during ischemia and reperfusion via increasing SP release. This pathway is independent of cardiomyocyte contractility. Furthermore, genetic ablation of the TRPV1 elicits compensatory changes related to enhancement of non-TRPV1-dependent SP release and SP receptor function to protect against ischemia/reperfusion injury. Our data may have important clinical implications given that sensory nerve function is impaired under certain pathophysiological conditions including diabetic and aging hearts, leading to impaired cardioprotection against ischemic injury. Furthermore, our data may lead to future investigation of the possibility of improving cardiac function by enhancing TRPV1 function and prompt future development of a new class of drugs for prevention and treatment of cardiac ischemia injury.

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25. Wang Y, Meyer JW, Ashraf M, Shull GE. Mice with a null mutation in the vanilloid type 1 (TRPV1) channel. TRPV1 is a nonselective cation channel that, when activated by capsaicin, lipid metabolites, noxious heat, or protons, causes the release of sensory neurotransmitters including substance P (SP) and calcitonin gene–related peptide from peripheral nerve terminals, leading to altered cardiovascular responses. The experiments presented in this study, which used isolated perfused hearts from gene-targeted TRPV1-null mutant and wild-type mice in a Langendorff perfusion apparatus, provide direct evidence for the first time that TRPV1 plays an important role in cardioprotection during ischemia and reperfusion via increasing SP release. This pathway is independent of cardiomyocyte contractility. Furthermore, genetic ablation of the TRPV1 elicits compensatory changes related to enhancement of non-TRPV1-dependent SP release and SP receptor function to protect against ischemia/reperfusion injury. Our data may have important clinical implications given that sensory nerve function is impaired under certain pathophysiological conditions including diabetic and aging hearts, leading to impaired cardioprotection against ischemic injury. Furthermore, our data may lead to future investigation of the possibility of improving cardiac function by enhancing TRPV1 function and prompt future development of a new class of drugs for prevention and treatment of cardiac ischemia injury.


