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ROLE OF TRPV1 CHANNELS IN ISCHEMIA –REPERFUSION INJURY OF MYOCARDIUM

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ABSTRACT

Transient receptor potential vanilloid 1 (TRPV1) channels are cation specific channel responsible for pain sensation. Besides its role in pain sensation, it plays a pivotal role in ischemia reperfusion injury of myocardium. Activation of transient receptor potential vanilloid 1 channel diminishes ischemia-reperfusion induced injury in myocardium. Sensory neurons innervating the myocardium express vast amount of transient receptor potential vanilloid 1 channels. During ischemic conditions, activation of TRPV1 channels on the perivascular nerves stimulates the release of calcitonin gene-related peptide and substance P to offer cardioprotection. Moreover, activation of TRPV1 channel helps to reduce production of the of free radicals and inflammatory cytokines, inhibits neutrophil infiltration, and increases the production of anti-inflammatory cytokines to diminish ischemia–reperfusion-induced tissue injury various organs including the heart. The current review highlights the potential role of TRPV1 channels and the signaling cascade in cardioprotection against ischemia–reperfusion injury.

KEY WORDS

TRPV1 channels, heart, ischemia, CGRP, substance P, Capsaicin

1. INTRODUCTION

Transient receptor potential vanilloid 1 (TRPV1) channels are part of TRP family which are a group of unique ion channels[1]. These ion channels are selectively permeable to H+, Na+, Ca2+, and Mg2+ and serve as cellular sensors for a wide range of chemical and physical stimuli[2]. Thus, TRP superfamily is cation specific ion channels and shows greater diversity in activation mechanisms and selectivities than any other group of ion channels. The TRP superfamily is divided into seven subfamilies: the five group 1 TRPs (TRPC, TRPV, TRPM, TRPN, and TRPA) and two group 2 subfamilies (TRPP and TRPML)[3]. TRP ion channels were first described in 1989 in Drosophila melanogaster[4]. TRP channels are widely distributed in many tissues and cell types. A number of them appear to be universally expressed, whereas others exhibit more restricted expression patterns. Besides the plasma membrane, TRP channels are also found in intracellular membranes[5].

Transient receptor potential vanilloid 1 channel comprised of six transmembrane helices per subunit with cytoplasmic amino and carboxy termini, a loop localized between fifth and sixth transmembrane domain and it exists in the form of tetrameric assemblies. It is having short, pore-forming hydrophobic stretch between the fifth and sixth transmembrane domains. TRPV1 is expressed in all sensory ganglia (DRG, TG, Vagal) and in small sensory C-and Aδ fibers, which may contain various neuropeptides including substance P (SP) and/or Calcitonin Gene-Related Peptide (CGRP)[6-9].

TRPV1 functions as a molecular heat sensing device. Rise in temperature above 43°C causes abrupt increase in inward current of ion channel[10]. This increase in

temperature not only produces a sensation of pain through direct activation of TRPV1, but it also produces neurogenic inflammation through the efferent release of pro-inflammatory neuropeptides[11]. The presence of TRPV1 in free nerve terminals in the skin allows us to detect nociceptive temperatures (> 43°C). However, these channels are exposed to a plethora of regulators that potentiate the channel's response to temperature[12].

The distribution of transient receptor potential vanilloid 1 channels in body includes different organs including heart, liver, lungs, kidney, intestine, and brain[13]. The primary pungent ingredient of hot chilli peppers, low pH and high temperatures and noxious stimuli can stimulate and activates transient receptor potential vanilloid 1 channels. Besides functioning as sensors of noxious heat, these channels are activated by various chemical agents including arachidonic acid metabolites, capsaicin, protons, and peptide toxins. TRPV1 channels are expressed on the ventricles of the heart, epicardial surface of the heart, endothelial cells, and vascular smooth muscle cells in cardiovascular system. In addition to that, these are also widely expressed on the sensory neurons innervating the myocardium[14].

Activation of TRPV1 channels from cardiac sensory nerves enhances the release of calcitonin gene-related peptide (CGRP) and substance P to provide cardioprotective actions[15, 16]. Recent studies on TRPV1 have exhibited the activation of TRPV1 diminishes ischemia-reperfusion-induced injury in several organs including brain, lungs, heart and kidney[16-17]. In addition to that, it has been observed that activation of these channels in the isolated rat hearts is responsible to initiate hypoxic preconditioning and ischemic post-conditioning. The current review highlights the potential role of TRPV1 channels and possible mechanism in attenuating ischemia–reperfusion injury in myocardium[18-19].

2. CARDIOPROTECTIVE EFFECTS OF TRPV1 CHANNEL ACTIVATION IN ISCHEMIA–REPERFUSION INJURY

Several efforts were made to identify the role of TRPV1 channel in cardiovascular system and various investigations from research have explored the potential role of TRPV1 channel activation in diminishing ischemia–reperfusion-induced myocardial injury[16, 17, 20, 21].

Wei and colleagues shown that decline in CGRP release due to metabolic syndrome-dependent reduction of TRPV1 channel expression led to higher extent of ischemia–reperfusion injury in the isolated mice hearts. They have demonstrated that hearts of diabetic mice showed increased attenuation in coronary flow, heart rate and left ventricular developed pressure (LVDP) whereas increased level of lactate dehydrogenase from perfusion as compared to the hearts isolated from normal mice in langendorff's perfused isolated heart preparation experiments. While, administration of CGRP (10^{-7} mmol/L) for 5-mins prior to 30-mins of global ischemia and 40-mins of reperfusion in both normal and diabetic mice hearts exhibited attenuation of ischemia-reperfusion injury of myocardium.

Pretreatment of capsaicin (potent TRPV1 channel agonist, 10^{-6}mol/L) for 5-mins before global ischemia demonstrated significant reduction in ischemia-reperfusion injury of normal hearts; however, this cardioprotective effect of capsaicin was not observed in diabetic mice hearts. The unresponsive effects of capsaicin in diabetic mice hearts may be partially due to the reduction in the number and functionality of myocardial TRPV1 receptors in the diabetic hearts. In spite of reduction in expression of TRPV1, exogenous CGRP administration demonstrated cardioprotective action in diabetic mice hearts; clearly points out the role of TRPV1 channel in cardioprotection along with downstream pathway of the CGRP[21].

Moreover, Zheng and his colleagues have demonstrated that excessive ischemia-reperfusion injury is the key manifestation of metabolic disorder due to reduction in the expression of nerve growth factor, TRPV1 channel expression, and release of CGRP and substance P in the isolated mice hearts. Adenovirus-mediated administration of the nerve growth factor gene significantly improved post-ischemic recovery, increased the expression of TRPV1 channels, and increased the release of CGRP; however, this is not the case for substance P, in the coronary effluent in normal and diabetic mice hearts. Whereas, administration of substance P receptor antagonist (RP67580) had no effect on nerve growth factor-mediated cardioprotective effects, indicating that substance P may not be involved in cardioprotection against ischemia-reperfusion injury. Moreover, it was observed that presence of CGRP antagonist ($CGRP_{8-37}$, 10^{-6} mol/L) significantly abolished cardioprotective effects offered

by nerve growth factor. Hence, it was suggested that nerve growth offered cardioprotective effects are mediated through CGRP release.

Administration of exogenous low-dose capsaicin (10^{-6} mol/L), 5-min prior to global ischemia led to significant improvement in post-ischemic cardiodynamic parameters including functional recovery in diabetic hearts, suggesting the cardioprotective role of TRPV1 channel upon activation. From all of these findings from experiments indicated that nerve growth factor offered restoration of TRPV1 channel and CGRP release may protect diabetic mice heart from ischemia-reperfusion injury[16].

Zhong and Wang shown that N-oleoyldopamine (2×10^{-9}M, TRPV1 agonist) administration in the Langendorff perfused hearts led to improvement in post ischemic cardiodyanmic parameters such as increase in LVDP, coronary flow, and +dP/dt against ischemia-reperfusion injury of myocardium. While cardioprotective effect was not observed in TRPV1$^{-/-}$mice hearts with TRPV1 agonist, emphasizing the role of TRPV1 channels in cardioprotection. Administration of TRPV1 agonist led to enhanced CGRP and substance P release in normal hearts in comparison with TRPV1 $^{-/-}$ hearts[15].

However, presence of chelerythrine (5×10^{-6} M, Protein kinase C [PKC] antagonist), tetrabutylammonium (5×10^{-4}M, nonselective K^+ channel antagonist), $CGRP_{8-37}$ (10^{-6} M), and RP67580 (10^{-6} M) significantly inhibited N-oleoyldopamine mediated cardioprotection. This concludes that activation of TRPV1 channel exhibits cardioprotection via promoting release of CGRP and substance P. All these inhibitors were administered 5-min prior to agonist administration and continued for 5-min after administration of agonist. Inhibition of cardioprotective effect of TRPV1 agonist by PKC inhibitor addition to perfusion suggests the critical role of PKC in TRPV1 offered cardioprotection. Various investigations have demonstrated that activation of PKC is responsible for phosphorylation of TRPV1 channel and thereby causing enhances release of CGRP and substance P from nerve ending. In addition to that, presence of K^+ channel inhibitors also demonstrated significant inhibition of cardioprotective effect of TRPV1 agonist; which suggests potential link between K^+ channel and TRPV1 channels.

Recently, some efforts also made to find out a link between TRPV1 and Protease-activated receptors (PARs) in cardioprotection and it has been proposed that Protease-activated receptors (PARs) comprise of 7 transmembrane domains G protein-coupled receptors that are activated by proteolytic cleavage of amino terminus of the receptor and act as sensors for extracellular proteases. Inflammation and injury response are widely modulated by Protease activated receptor 2 (PAR2). Serine proteases including trypsin, coagulation factors VII_a and X_a, tissue kallikreins, and mast cell tryptase are responsible for activation of PAR2. Amadesi and colleagues have observed that blood vessels, the perivascular nerves and the cardiomyocytes are abundantly expresses TRPV1 channel along with PAR2. Administration of Synthetic peptide (SLIGRL) (10^{-7} M, PAR2 agonist) for 15-mins exhibited significant improvement in LVDP, +dP/dt, -dP/dt, and coronary flow rate; whereas these cardioprotective effects were abolished in presence of PKA inhibitor, PKC inhibitor and CGRP inhibitors.[22,23] All these inhibitors were administered 5-mins prior to agonist administration and continued for 5-mins after agonist perfusion. These results indicate pivotal role of PKA, PKC signaling, and release of CGRP and substance P in mediating cardioprotection. Furthermore, the administration of SLIGRL significantly increased the release of CGRP and substance P in the normal hearts that was not observed in TRPV1-/- mice hearts. This emphasis on other finding of possible involvement of TRPV1 channel in PAR2 activation offered cardioprotective effects[17]. Previous investigation of Amadesi et al also demonstrated that activation of PAR2 sensitizes TRPV1 channel via PKC signaling. Thus, it may be proposed that PAR2 activation probably stimulates TRPV1 channels via PKA/PKC signaling to enhance the release of CGRP and substance P to provide cardioprotective effects[24].

2.1 Capsaicin and Cardioprotection

Capsaicin is pungent ingredient from hot chili peppers. Qin et al reported that capsaicin treatment significantly improves myocardial performance in terms of LVDP and heart rate in in vivo model of ischemia-reperfusion injury. However, these protective effects markedly reduced in the presence of capsazepine and S-3144 (substance P receptor antagonist) significantly diminish cardioprotective action mediated by capsaicin. Capsazepine is an antagonist of TRPV1 channel and capsazepine and S-3144 were administered into the rat left ventricle via the right carotid artery, 5-mins and 10-mins prior to global ischemia. This result suggests that activation of TRPV1 channels during ischemia may cause

enhanced release of substance P and thereby reducing detrimental effects of ischemia-reperfusion injury. They have also found that post-ischemic infarct size of hearts treated with capsaicin was significantly lowered than normal hearts and this effect were reduced in hearts treated with capsazepine and S-3144(administered into the rat left ventricle via the right carotid artery, 5-mins and 10-mins prior to global ischemia), indicating the protective effects are mediated via activation of TRPV1 channels[25,26].

Wang and Wang found a predominant role of endogenous substance P, but not CGRP, in providing cardioprotection during ischemia-reperfusion injury. They have identified that the extent of ischemia-reperfusion induced myocardial injury is higher in TRPV1 -/- mice hearts in comparison with the normal heart. This in turns suggests that intact TRPV1 channel tends to lower ischemia-reperfusion induced myocardial injury. Furthermore, pre-treatment with capsazepine (10^{-6} mol/L), 5-mins prior to global ischemia, enhanced ischemia-reperfusion-induced myocardial injury in the isolated normal hearts, indicating the involvement of TRPV1 channels in reducing ischemia–reperfusion injury. On other hand, exogenous administration of CGRP (10^{-7} mol/L) and substance P (10^{-6} mol/L) 5-mins prior to global ischemia exhibited significant improvement in post-ischemic cardiodynamics parameters in both isolated TRPV1 -/- and normal mice hearts; suggesting CGRP and substance P are having cardioprotective potential which could be independent of TRPV1 channel activation. The investigators further supported the critical role of substance P in ischemia-reperfusion injury by demonstrating an increase in substance P release during ischemia–reperfusion that was significantly attenuated in the presence of capsazepine. Although substance P was also released during ischemia–reperfusion from TRPV1 -/- hearts, the release was of smaller magnitude and capsazepine pretreatment did not affect its release. It probably suggests that TRPV1 channels are not the sole source of substance P release, and there might exist TRPV1-independent pathway for its release during ischemia-reperfusion injury (Figure 1)[20].

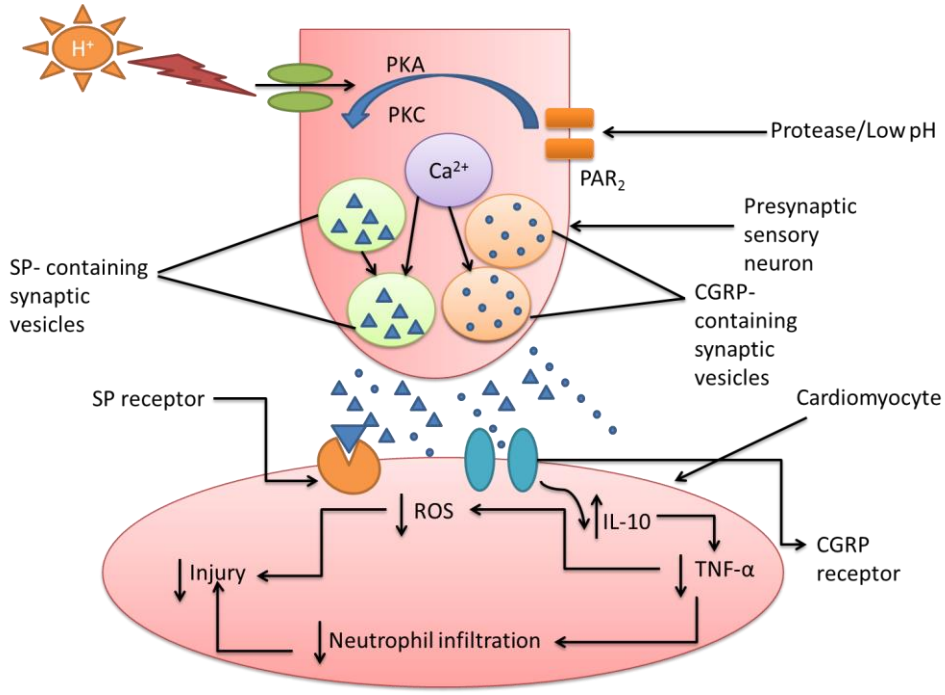

Figure 1: Low pH or proteases activate PAR2 to stimulate TRPV1 channels via PKA/PKC signaling which further activate release of CGRP and substance P release from the synaptic vesicles via activation of intracellular Ca^{2+}.CGRP and substance P bind to the respective receptors to increase the release of anti-inflammatory cytokine, IL-10 which in turn reduces the TNF-a levels. Reduction in the TNF-a level may decrease ROS and neutrophil infiltration to attenuate ischemia-reperfusion injury in the respective tissues. CGRP indicates calcitonin gene–related peptide; IL- 10, Interleukin 10; PAR2, protease-activated receptor 2; PKA, protein kinase A; PKC- Protein kinase C; ROS, Reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

3. CARDIOPROTECTIVE EFFECTS OF TRPV1 CHANNEL ACTIVATION IN CONDITIONING-INDUCED CARDIOPROTECTION

Now days, various investigations have identified that activation of TRPV1 channels play a pivotal role in conditioning-induced cardioprotective effects[19]. Lu et al demonstrated that TRPV1 channels activation plays an important and critical role in cardioprotection via hypoxic preconditioning in the isolated rat hearts. They have observed that presence of capsazepine (1 µM, TRPV1 antagonist) significantly diminished hypoxic preconditioning-induced cardioprotective effects. This is indicative of cardioprotective role of TRPV1 channels. Recently, Gao and coworkers revealed the role of TRPV1 channel in mediating remote ischemic post-conditioning induced cardioprotection. The authors reported that remote ischemic postconditioning-induced cardioprotective effects were abolished in the presence of CGRP8-37 (2 mg/kg, 2 minutes before reperfusion) and RP-67580 (5 mg/kg, 5 minutes before reperfusion), suggesting the involvement of CGRP and substance P in mediating remote ischemic post-conditioning induced cardioprotection. In addition, remote ischemic post-conditioning remarkably augmented the levels of CGRP and substance P in the plasma and the heart that was abrogated in the presence of capsazepine (3 mg/kg, 10 minutes before reperfusion). Moreover, remote ischemic postconditioning also increased mRNA expression, along with an increase in CGRP and substance P levels in the dorsal root ganglion. This suggests that remote ischemic postconditioning stimulus possibly activates TRPV1 channels and increases the synthesis and release of CGRP and substance P in the dorsal root ganglion, which may be released into the plasma and activate the corresponding myocardial receptors to produce cardioprotection[18,19].

4. FINDINGS AND DISCUSSION

Based on above investigations cited, it is believed that TRPv1 channel activation plays a pivotal role in cardioprotection against ischemia-reperfusion injury of myocardium[25,26]. Based on various scientific discussions, it has been concluded till date that activation of these channels causes discharge of CGRP and substance P from sensory nerve ending innervating the myocardium which in turns protect the myocardium against injury caused by ischemia-reperfusion[27,28]. Various investigators have utilized vast pharmacological agent to elucidate mechanism of cardioprotection offered by TRPV1 channel including N-oleoyldopamine, capsaicin, resiniferatoxin, CGRP8-37, RP-67580, capsazepine, and TRPV1 knockout mice. They have evaluated signaling cascade responsible for PAR2-dependent TRPV1 channel activation and it was observed that PKA/PKC signaling mediates stimulation of TRPV1 channel via activation of PAR2; which in turn enhances release of CGRP and substance P from nerve terminal[5,7,11]. Though it has been well understood and declared that CGRP and SP attenuate ischemia-reperfusion injury of myocardium, question remains unanswered regarding association of TRPV1 with CGRP and substance P offered cardioprotection signaling. Recent research suggests that CGRP release from nerve ending is responsible for inhibition of reactive oxygen species, which in turn reduces free radical formation, neutrophil infiltration, and production of other inflammatory mediators[29,30]. These lead to increase the tissue tolerance against ischemia-reperfusion injury. However, detail investigations are required to explore the signaling cascade involved in TRPV1 channel activation, CGRP and substance P release, reduced production of inflammatory cytokines[30].

5. CONCLUSION

Cardiovascular disease (CVD) is considered as the leading cause of mortality in today's industrialized world, among all CVDs, acute myocardial infarction (AMI) accounting for a vast portion of CVD-associated mortality. Timely reperfusion is considered as a choice of therapy in clinical setting of AMI, although necessary to rescue ischemic tissue, restoration of blood flow can paradoxically exacerbate cell death (rather than initiate salvage) in populations of ischemic myocytes, a phenomenon termed lethal ischemia-reperfusion (I/R) injury. The volume of myocardium rendered necrotic following I/R (i.e., myocardial infarct size) is a primary determinant of mortality and morbidity associated with AMI. Indeed, decades of preclinical and clinical investigation have been devoted to: (I) investigating the mechanisms of I/R injury, and (II) identifying mechanisms-based therapies to augment the benefits of early reperfusion and reduce myocardial infarct size. Despite this substantial investment of time and resources, no advances have, to date, been successfully transformed into clinical practice.

Activation of TRPV1 channels attenuates ischemia-reperfusion-induced injury in a variety of organs including heart, kidney, lungs, and brain possibly via enhancing the discharge of CGRP and substance P. In turn, CGRP may reduce the production of free radicals, neutrophil infiltration, and other inflammatory mediators to reduce ischemia-reperfusion injury. Nevertheless, further studies are warranted to explore the signaling cascade involved in TRPV1 channel activation, CGRP and substance P release, and reduced generation of inflammatory cytokines during ischemia-reperfusion tissue injury.

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AUTHOR CONTRIBUTIONS

Anita Mehta conceived the idea of writing the review, did technical checking of the manuscript. Mihir Patel did the literature survey and compilation of the studies. This study is a part of Ph.D. thesis of Mihir Patel and was supported by L. M. College of Pharmacy and C. U. Shah University.

CONFLICTS OF INTERESTS

The authors declared no conflicts of interest.

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