Life Sciences 155 (2016) 140–146

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

# Unraveling the role of adenosine in remote ischemic preconditioning-induced cardioprotection

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ARTICLE INFO

*Article history:*
Received 2 March 2016
Received in revised form 3 May 2016
Accepted 4 May 2016
Available online 6 May 2016

*Keywords:*
Adenosine
Cardioprotection
Remote ischemic preconditioning
Neurogenic

ABSTRACT

Remote ischemic preconditioning (RIPC) induced by alternate cycles of preconditioning ischemia and reperfusion protects the heart against sustained ischemia-reperfusion-induced injury. This technique has been translated to clinical levels in patients undergoing various surgical interventions including coronary artery bypass graft surgery, abdominal aortic aneurysm repair, percutaneous coronary intervention and heart valve surgery. Adenosine is a master regulator of energy metabolism and reduces myocardial ischemia-reperfusion-induced injury. Furthermore, adenosine is a critical trigger as well as a mediator in RIPC-induced cardioprotection and scientists have demonstrated the role of adenosine by showing an increase in its levels in the systemic circulation during RIPC delivery. Furthermore, the blockade of cardioprotective effects of RIPC in the presence of specific adenosine receptor blockers and transgenic animals with targeted ablation of $A_1$ receptors has also demonstrated its critical role in RIPC. The studies have shown that adenosine may elicit cardioprotection via activation of neurogenic pathway. The present review describes the possible role and mechanism of adenosine in mediating RIPC-induced cardioprotection.



**Contents**



## 1. Introduction

Ischemia is inadequate blood supply to the tissues that leads to oxygen, glucose starvation and disturbs the normal cellular metabolism. Although, reperfusion has the tendency to salvage the myocardium, yet restoration of blood flow has the potential to exaggerate tissue injury [23]. Reperfusion injury often counterbalances the optimum salvage of the myocardium achieved during cardiac surgery/percutaneous coronary intervention/cardiac transplantation. Therefore, various treatment strategies have been adopted to condition the myocardium and alleviate myocardial ischemia-reperfusion-induced injury in the patients undergoing various cardiovascular interventions. Based on the time period of delivery of the remote conditioning stimulus (brief episodes of ischemia-reperfusion) i.e. before, during or after sustained

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http://dx.doi.org/10.1016/j.lfs.2016.05.009
0024-3205/

ischemia, the treatment strategy can be categorized into remote ischemic preconditioning [31], remote ischemic perconditioning [24] or remote ischemic post-conditioning [9], respectively.

Murry and co-workers first discovered the concept of ischemic preconditioning, whereby brief episodes of ischemia-reperfusion to the left circumflex coronary artery conferred protection against sustained ischemia-reperfusion injury in the left ventricle [45]. Furthermore, Przyklenk et al. introduced the concept of intra-cardiac preconditioning (remote ischemic preconditioning), whereby short episodes of ischemia-reperfusion to the left circumflex artery salvaged the myocardium against sustained occlusion of left anterior descending coronary artery [51]. Later on, Gho and co-workers demonstrated that brief ischemia-reperfusion episodes in other remote tissues including mesenteric arteries protect the myocardium against sustained lethal insult [70]. Subsequently, Birnbaum et al. reported that in vivo remote preconditioning stimulus can also be delivered non-invasively by lower limb ischemia-reperfusion cycles [5]. Dickson et al. demonstrated that preconditioning effect can be transferred between rabbit hearts via whole blood/coronary effluent transfusion of the preconditioned animals indicating that the remote protection is possibly initiated via humoral mechanism [11–13]. Afterwards, Bøtker et al. demonstrated that remote ischemic preconditioning strategy can be translated clinically and has the potential to significantly increase myocardial salvage in clinical set-ups in patients undergoing percutaneous coronary intervention [6]. Remote ischemic preconditioning (RIPC) is a therapeutic treatment strategy whereby alternate cycles of preconditioning ischemia and reperfusion are delivered to a remote organ (other than heart) to confer protection in the target organ i.e. heart against sustained ischemia-reperfusion-induced injury [52,53,70,71]. RIPC technique has also been employed clinically for alleviating myocardial injury in patients undergoing various surgical interventions including coronary artery bypass graft surgery, abdominal aortic aneurysm repair, percutaneous coronary intervention and heart valve surgery [6,52,67]. The neurogenic theory hypothesizes that RIPC stimulus induces the release of endogenous mediators which stimulate the afferent nerve fibres and consequently relay signals to the efferent nerve fibres terminating at the heart to provide cardioprotection [39]. On the other hand, the humoral theory postulates that RIPC stimulus induces the release of endogenous substances into the bloodstream that reach the heart to exert cardioprotective effects [22,39].

Adenosine is an endogenous purine nucleoside that modulates cellular homeostasis and is released in large amounts in response to metabolic stress including ischemia [21]. Adenosine acts on G-protein coupled receptors namely $A_1$, $A_{2a}$, $A_{2b}$, $A_3$ for modulating various biochemical processes and transducing a variety signals in the cells. The cardioprotective effects of adenosine are predominant due to their abundant presence in the heart [46]. Adenosine is a master regulator of energy metabolism and adenosine agonists have shown to reduce myocardial ischemia-reperfusion-induced injury [60]. Furthermore, adenosine is a critical mediator of ischemic preconditioning and renders the heart resistance against sustained ischemia-reperfusion-induced injury [28,34]. Transient RIPC episodes also result in the release of substances including adenosine to activate a cascade of cardioprotective pathways and protect the myocardium against sustained-ischemia reperfusion-induced injury [15,25,38,48,57,59]. The present review describes the role and mechanism of adenosine in mediating RIPC-induced cardioprotection.

## 2. Clinical applications of RIPC

RIPC has been verified as an efficient cardioprotective strategy in animal models and has also been translated into clinical settings [6]. In clinics, RIPC stimulus is delivered in the form of inflation of the blood pressure cuff tied on the upper arm 20 mm greater than the systolic blood pressure followed by deflation of the cuff. This cycle is repeated for 3–-4 times to precondition the heart and increase the resistance against sustained ischemia [67]. RIPC stimulus in the form of brief forearm ischemia is easily delivered in the clinical settings as it is a noninvasive, safe technique and skeletal muscles are relatively more resistant to the ischemic injury [63] in comparison to other organs including kidney and liver. RIPC possesses the ability to reduce myocardial injury in patients undergoing cardiac interventions including coronary artery bypass grafting [7,67,72]. Furthermore, RIPC has also shown to reduce major adverse cardiac and cerebral events after 6 years post elective percutaneous coronary intervention [10]. Besides, bearing the tendency to alleviate myocardial injury, RIPC also protects against renal transplantation-induced ischemia-reperfusion injury and enhanced the early recovery of renal function in the recipients [65]. RIPC also possesses the potential to mitigate acute kidney injury [69], improve cognitive performance [26] in patients undergoing cardiac surgeries. In addition, RIPC prevents contrast induced kidney injury in diabetic patients undergoing coronary artery angiography [56].

## 3. Adenosine in RIPC

### 3.1. Evidences

The precise involvement of adenosine receptors in transducing RIPC signals to the myocardium has been demonstrated [15,25,38,48,57,59]. Pell et al. demonstrated that a single cycle of 10 min renal preconditioning ischemia followed by 10 min of reperfusion afforded myocardial protection against sustained occlusion-reperfusion of the left coronary artery in in vivo rabbit model of myocardial infarction. However, remote preconditioning-induced cardioprotection was significantly inhibited in the presence of 8-(p-sulfophenyl)-theophylline, 8-SPT (non-selective adenosine receptor blocker) suggesting the involvement of adenosine receptors in mediating acute preconditioning of the myocardium [48]. Takaoka et al. also described that remote renal preconditioning (10 min renal artery occlusion-20 min reperfusion) significantly reduces the infarct size and improves myocardial energy metabolism (delayed decrease in ATP and phosphocreatine levels, preserved pH) in rabbit hearts exposed to sustained ischemia-reperfusion (40 min coronary occlusion-120 min reperfusion) insult. However, 8-SPT pretreatment considerably inhibited RIPC-induced improvement in myocardial energy metabolism. Furthermore, a sharp rise in adenosine levels was reported in the carotid artery following remote renal preconditioning stimulus suggesting that RIPC elicits cardioprotective effects via adenosine-dependent mechanism and adenosine possibly serves as a trigger to induce cardioprotection [59]. Furthermore, Ding et al. reported that remote renal preconditioning (10 min ischemia-10 min reperfusion)-induced cardioprotective effects in rabbits were significantly inhibited by renal nerve resection suggesting that renal nerve critically participates in mediating remote renal preconditioning-induced cardioprotection. Remote renal preconditioning ischemia also evoked adenosine RNA discharge from the renal afferents that was attenuated by prior 8-SPT pretreatment indicating that adenosine is possibly released during preconditioning, which consequently activates the renal afferents to induce cardioprotection. This suggests that remote renal preconditioning causes local increase in adenosine levels, which in turn activates the renal afferents to induce cardioprotective effects [14].

Apart from the involvement of adenosine in producing remote renal preconditioning-induced cardioprotective effects, adenosine is also potentially involved in mediating cardioprotective effects in other forms of preconditioning including mesenteric preconditioning [38] and limb preconditioning [15]. Liem et al. demonstrated that 15 min of mesenteric artery occlusion preceding 60 min of coronary artery occlusion significantly reduced the infarct size in rats that was abolished in the presence of 8-SPT (non-selective $A_1$-receptor antagonist), MRS-1191 (selective $A_3$-receptor antagonist) and hexamethonium (ganglion blocker) suggesting the involvement of neurogenic pathway and activation of adenosine $A_1$ and $A_3$ receptors in mediating RIPC-induced