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Review Article

Abrogated cardio protective effect of ischemic preconditioning in hyperhomocysteinemia and hypertrophy

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ABSTRACT

Coronary heart disease has almost affected the mankind throughout history. During the last century, this disorder has emerged as a leading cause of death all over the world. Ischemia contributes in the development of myocardial infarction, stroke, peripheral vascular insufficiency and hypovolemic shock. Reperfusion enhances the tissue injury produced by ischemia alone. Cellular damage after reperfusion of formerly viable ischemic tissues is known as ischemia–reperfusion (I–R) injury. Ischemic preconditioning is known as the phenomenon in which the short intermittent cycles of ischemia and reperfusion has shown to improve myocardium against subsequent prolonged ischemia–reperfusion (I–R)induced injury. Experimentally, preconditioning has revealed to improve ventricular function and to decrease apoptosis and myocardial neutrophil accumulation after ischemia reperfusion injury. Recently, ischemic preconditioning has been demonstrated to have a beneficial effect on recovery of right ventricular contractility in coronary artery bypass grafting and to improve liver injury during hepatic resection. The cardioprotective role of ischemic preconditioning is well established, but it is lost in various clinical conditions such as hyperhomocysteinemia and cardiac hypertrophy. In this review, we have discussed the various signaling pathways which are involved in abrogated preconditioning in hyperhomocysteinemia and cardiac hypertrophy.

1. Introduction

Coronary heart disease is a growing problem, affecting the mankind across the world. It is the most common cause of cardiovascular death and stroke.[1] Myocardial ischemia is defined as an insufficient blood supply to the myocardium.[2] Although early reperfusion protects the myocardium from damage, yet reperfusion after a prolonged ischemic insult causes tissue injury which is known as ischemia reperfusion (I/R) injury.[3,4] It is characterized by a cascade of adverse events i.e. metabolic disorder, cell death and local inflammatory responses that leads to myocardial ultrastructural changes and subsequently myocardial systolic and diastolic dysfunction.[5–7] It has been reported that reactive oxygen or nitrogen species (ROS or RNS), including superoxide radicals, hydrogen peroxide, hydroxyl radicals, singlet oxygen, nitric oxide, and peroxynitrite ($ONOO^-$) are majorly responsible for myocardial I–R injury.[8,9]

1.1. Ischemic preconditioning and its molecular mechanism

This concept of preconditioning to prevent I/R injury was given by Murry and coworkers in 1986. They suggested that brief intermittent periods of sublethal ischemia followed by reperfusion have a protective effect on myocardial tissue against prolonged ischemic insult which is called "ischemic preconditioning" (IPC).[10,11] Ischemic preconditioning is a biphasic phenomenon, an early phase which starts within minutes and wanes off gradually within 2–3 h and called as classical preconditioning.[12,13] The other is late phase which is delayed to 12–24 h after the ischemic stress and lasts up to 3–4 days and called as late phase

Abbreviations: (I–R), ischemia–reperfusion injury; IPC, ischemia preconditioning; ROS, reactive oxygen species; RNS, reactive nitrogen species; ($ONOO^-$), peroxynitrite; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidyl-inositol 3,4,5-triphosphate; PIP2, phosphatidyl inositol 3,4-biphosphate; PDK1, phosphoinositide-dependent kinase; mitoK_{ATP}, mitochondrial ATP-sensitive potassium channels; DAG, diacylglycerol; IP3, inositol triphosphate; PKC, protein kinase C; mPTP, mitochondrial permeability transition pore; GSK-3β, glycogen synthase kinase-3β; Hhcy, hyperhomocysteinemia; LDL, low density lipoproteins; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor NF-kappa-B; CK, creatinine kinase; LDH, lactate dehydrogenase; JAK, Janus kinase; Akt, protein kinase B; ATP, adenosine triphospahte; DOCA, deoxycorticosterone acetate; EAAT2, excitatory amino acid transporter 2; SHR, spontaneously hypertensive rats.

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preconditioning or second window of protection.[14,15] The early phase IPC protects only against the myocardial infarction but the late phase IPC protects against myocardial stunning as well.[16,17]

Preconditioning causes the generation and release of various endogenous ligands, thus leading to activation of their corresponding receptors.[18] The endogenous ligands generated and released during ischemia and reperfusion are adenosine,[19] bradykinin,[20,21] opioids,[22] norepinephrine[23] and acetylcholine.[24] They bind to their respective G-protein coupled receptors and initiates a cascade of signal transduction which leads to activation of phosphatidylinositol 3-kinase (PI3K)[25] and phospholipase C.[26]

Activated PI3K generates phosphatidyl-inositol 3,4,5-triphosphate (PIP3) from cell membrane lipid phosphatidyl inositol 3,4-biphosphate (PIP2) leading to activation of phosphoinositide-dependent kinase (PDK1) and subsequent activation of protein kinase B (Akt) and p70S6-kinase.[27,28] PI3K/Akt activation reported to upstream PKC,[29] GSK3β,[30] generation of NO and activation of mitochondrial ATP-sensitive potassium channels (mitoK_{ATP}).[31,32]

The activated phospholipase C leads to generation of two second messengers i.e. diacylglycerol (DAG) and inositol triphosphate (IP3) by hydrolysis of PIP2. The DAG activates protein kinase C (PKC) by translocating it from cytosol to perinuclear membrane.[33,34] PKC activation has been shown to be important in opening of mitoK_{ATP}.[35] PKC_{ε} as well as PKC_{δ} has been demonstrated to mimic preconditioning due to opening of mitoK_{ATP}.[36] As potassium enters the mitochondria, it causes them to release free radicals, known as reactive oxygen species (ROS).[37] ROS generation during preconditioning also activates PKC.[38,39] Although a large burst of ROS lead to cell damage, a moderate release of ROS during nonlethal short episodes of ischemia, play a significant triggering role in the signal transduction pathways of IPC.[40] PKC_{ε} also forms a complex with mitochondrial permeability transition pore (mPTP),[41,42] which leads to decrease in release of cytochrome C and apoptotic cell death.[43,44]

More recent interest has focused on glycogen synthase kinase-3β (GSK-3β), phosphorylated (and hence inactivated) by other kinases, including Akt and p42/p44 MAPK/ERK.[45] GSK-3β plays a significant role in apoptosis and necrosis of cardiomyocytes.[46] Experimental studies proved that GSK-3β confers cardioprotective effects through its potential mitochondrial effects including inhibition of mPTP's opening and control of mitochondrial adenine nucleotide transport through outer mitochondrial membrane.[47–49]

Although preconditioning provides a remarkable cardioprotection, its effectiveness is attenuated in some animal models of diseases, including hyperhomocysteinemia and cardiac hypertrophy due to alteration in intracellular signaling relevant to cytoprotection and thus myocardial responses to preconditioning[50] (Fig. 1).

2. Methods

2.1. Literature search

A systemic and thorough literature search on ischemia preconditioning for hyperhomocysteinemia and cardiac hypertrophy was performed. The existing scientific information was assessed from several reachable databases, such as PubMed US national Library of Medicinal database and journals indexed in like Elsevier, Springer, Scopus etc. The present review literature includes all relevant information regarding ischemia preconditioning and its abrogated protective effect in hyperhomocysteinemia and hypertrophy. A well organized and targeted database search was obtained by using certain text keywords, such as ischemia preconditioning attenuated cardio protection, replacing the disease name for each new search. The main emphasis was given on the mechanisms involved in the abrogated cardio protective effect of preconditioning.

2.2. Data collection and extraction

The entire manuscript was screened by three reviewers independently. Furthermore, an ineligible publication was excluded from the manuscript by the authors.

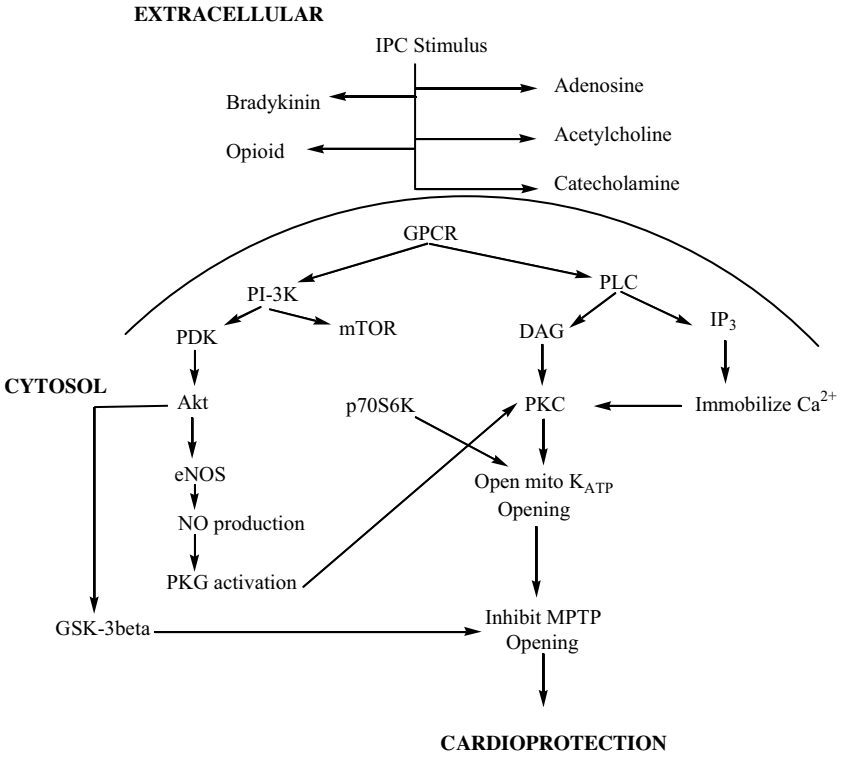

Fig. 1. Molecular mechanism of ischemia preconditioning.

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