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Cardioprotective triggers of ischemic preconditioning

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ABSTRACT

Myocardial ischemia is a condition in which the coronary blood flow to the myocardium is abridged resulting in deficient oxygen and nutrients supply to the heart. Reperfusion to an ischemic myocardium often results in lethal myocardial injury. The brief episodes of ischemia and reperfusion given before prolonged ischemia and reperfusion denotes preconditioning. In this review we have discussed the phenomenon of cardioprotection against ischemia reperfusion injury with various cardioprotective mechanisms contributed by ischemic preconditioning. Classical and delayed preconditioning has been described in this review. The protective effects of ischemia/perfusion cycles are evident within minutes after the insult and persist for 2-3 hours known as classical preconditioning or first window of protection (FWOP). The apparent approximately 24 hours after initial preconditioning and it can persist for up to 72 hours is known as delayed preconditioning or second window of protection (SWOP). Ischemic preconditioning activates some pharmacological cardioprotective endogenous or exogenous triggers such as mitochondrial K-ATP channel, adenosine, bradykinin, acetylcholine, nitric oxide (NO) and activation of protein kinase-c (PKC) and inhibition of mitochondrial permeability transition pore (MPTP). In this review, we have critically discussed the various triggers and their signalling pathways involved in the modulation of cardioprotective potential of ischemic preconditioning.

Keywords: Ischemic Preconditioning, PKC, Triggers, mPTP, FWOP etc.

INTRODUCTION

Ischemic heart diseases have been remarked as the primary cause of morbidity and mortality worldwide. The deprived blood flow followed by inadequate oxygen and nutrient supply renders the heart to be ischemic and early reperfusion is necessary for maintaining viability and protecting the heart against myocardial infarction. However, reperfusion after a period of ischemia produces a marked damage in coronary arteries and myocardial tissues that ultimately results in cardiac dysfunction, known as ischemia–reperfusion (I/R) injury [1]. Ischemic preconditioning can be referred to as the ability of short periods of ischemia and reperfusion to make the myocardium more resistant to a subsequent ischemic insult [2]. The preconditioning concept is playing a important role in cardiovascular research. Ischemic preconditioning was originally described in a landmark 1986 by Murry and associates [3]. Ischemic preconditioning has been well known to protect the heart against I/R injury and it is one of the most reproducible cardioprotective phenomenon to reduce I/R-induced myocardial infarct size [4]. This cardioprotective effect of ischemic preconditioning was independent of changes in transmural myocardial blood flow proposed that the effect was a result of rapid metabolic adaptation of the ischemic myocardium. The wide reproducibility of this phenomenon using a variety of preconditioning protocols in a number of species and experimental preparations and with a number of endpoints of protection, rapidly led to ischemic preconditioning being established as a “gold

standard" for cardioprotection. Prior to this 1986 discovery, the best pharmacological treatments for the protection of cardiac muscle from infarction only preserved 10-20% of tissue compared to the 75% protection afforded by preconditioning [5]. Ischemic preconditioning has been associated with two distinct phases of myocardial protection such as classic phase known as first window of protection (FWOP) and delayed phase, referred to as second window of protection (SWOP) Numerous experimental and clinical studies revealed that the preconditioning mediated cardioprotection is markedly suppressed in some pathological conditions such as hypercholesterolemia, hyperglycemia, hypertension, cardiac hypertrophy, aging, obesity and hyperhomocysteinemia [6]. In the present review, the various types of endogenous triggers and mediators involved to induce cardioprotective potential of ischemic preconditioning have been delineated.

CLASSICAL AND DELAYED PRECONDITIONING

In classical preconditioning, the protective effects of ischemia/perfusion cycles are evident within minutes after the insult and persist for 2-3 hours and also called FWOP [7]. Classical preconditioning is independent of protein synthesis, and is therefore dependent upon existing cellular pathways. It involves the direct modulation of energy supplies, pH regulation, Na+ and Ca2+ homeostasis and caspase inactivation [8]. Investigations have shown many triggers can activate classical ischemic preconditioning, including agonists of G protein-coupled receptors [9], opioids [10], norepinephrine [11], adenosine [12], potassium ATP channel (KATP) openers, such as diazoxide, pinacidil [13], succinate dehydrogenase inhibitors, such as 3-nitropropionic acid [14], and volatile anesthetics, such as sevoflurane and isoflurane [15]. With classic preconditioning, a trigger event, such as brief ischemia, activates a number of intracellular pathways that lead to the protection of cell. The actual sequence of these pathways has not been determined, but some components of the cascade have been identified. G-coupled receptors, for example, activate the epsilon (ε) isoform of protein kinase C (PKC-ε) [16,17], which has been involved in preconditioning. It has been noted that the PI3K activates the serine/threonine kinase which inactivates the pro-apoptotic kinase glycogen synthase kinase-3 (GSK-3) via phosphorylation [18]. Phosphorylation of GSK-3, in turn, inhibits the opening of the mitochondrial permeability transition pore (mPTP). Cell apoptosis or necrosis often occurs during reperfusion due to opening of the mPTP. Cytochrome c and apoptotic-inducing factor (AIF) are both released through the mPTP during ischemic reperfusion, leading to the activation of caspase and caspase-independent apoptotic pathways [19,20]. KATP channels are key intracellular triggers of early ischemic preconditioning. Delayed or late preconditioning becomes apparent approximately 24 hours after initial preconditioning and it can persist for up to 72 hours and known as SWOP, "delayed preconditioning," or "late phase preconditioning" [7]. The triggers for delayed preconditioning are similar to classical preconditioning. NO has been determined to have no effect on classical preconditioning and is a trigger specific only for delayed preconditioning [21]. Endogenous preconditioning agents also initiate delayed preconditioning and include adenosine agonists, bradykinin, opioids, NO donors, acetylcholine and norepinephrine [21]. Exogenous agents that activate the delayed preconditioning pathways include, diazoxide, nicorandil, some hypercholesterolemic agents, and volatile anesthetics [22]. A major conceptual development in delayed preconditioning was the recognition that autacoid factors released during preconditioning play an important role in eliciting the late-appearing adaptive response. Multiple studies using either ischemic preconditioning or pharmacological triggers of delayed protection have highlighted the involvement of activation of PKC [23,24,25], the JAK/STAT signaling pathway [26], p38 MAPK [27,28,29], PI3K and p70s6 kinase and p42/p44 MAPK/ERK [29]. It is clear that delayed preconditioning recruits multiple signaling pathways that are highly dependent on the nature of the priming stimulus, e.g., transient ischemia or application of specific receptor ligands. The activation of the transcription factor NF-B occurs by dual serine and tyrosine phosphorylation of the inhibitor protein IKB by both PKC and tyrosine kinases. The cytoprotection related proteins induced by NF-B-regulated gene expression include inducible NOS (iNOS) and cyclooxygenase- 2 (COX-2). Inducible NOS-derived NO appears to regulate the activation of COX-2 in the preconditioned myocardium, determining a pattern of prostanoid generation that is critical for the appearance of a cardioprotected phenotype [30].

TRIGGERS OF ISCHEMIC PRECONDITIONING

Adenosine

The first insight into IPC's mechanism discovered that activation of the G_i-coupled adenosine A_1 receptor triggered IPC's protection. It has been reported that an adenosine receptor antagonist could block IPC's protection and also showed that infusion of adenosine or the A_1-selective agonist R (−)-N^6-(2-phenyl-isopropyl) adenosine (PIA) in lieu of brief ischemia could duplicate IPC's protection. It was proposed that endogenous adenosine released during the brief ischemia of the IPC protocol activated A_1 adenosine receptors leading to a preconditioned phenotype [31]. Adenosine mediates its different cardiovascular actions via four known receptor subtypes (A1, A2A, A2B and A3). All are expressed in different cell types of the heart and blood vessels, but A1A receptors (A1ARs) and A2ARs are

expressed only in adult ventricular myocytes [32,33]. According to Liu and Hofmann [34], A1AR dependent p38 MAPK signalling can stimulate cardiac protein phosphatise activity. Moreover it has been noted that ARs also activate P13 kinase via tyrosine kinase activation. This activates Akt/PKB which in turn results in phosphorylation of BAD and phosphorylation and inactivation of GSK3b which improve cell survival [35]. It has been noted that adenosine activates the ERK1/2 leads to cardioprotection [36]. A number of studies support A2AR mediated cardioprotection during ischemia–reperfusion. Vinten-Johansen and colleagues have reported A2AR dependent protection by limiting the injurious effects of neutrophil activation and proapoptotic signalling [37]. A3ARs have been recently identified and cloned [38]. This subtype has been uniformly shown to mediate cardioprotective effects. Although their expression in cardiomyocytes has not been directly identified, A3ARs have been identified in human eosinophils [39] Although one way of affording cardioprotection is the inhibition of resident mast cell degranulation [36].

Bradykinin

Bradykinin (BK) is one of the important autacoids released by ischemic myocardium and appears to be the principle endogenous trigger of preconditioning. It binds to GiPCRs, leading to the activation of PI3-K, phosphorylation of Akt and ERK1/2 (without the involvement of EGFR), generation of nitric oxide (NO), activation of PKG and opening of mitochondrial KATP. The redox signaling by ROS leads to PKC activation which is thought to result in preconditioning. This is in contrast to adenosine which activates PKC directly, by passing the redox signaling pathway [40]. NO generation occurs by activation of BK receptors on the endothelial cells with subsequent calcium mediated NO production via nitric oxide synthase (NOS). NO activates guanylyl cyclase to produce cGMP which in turn stimulates PKG [41,42,43]. The activation of BKB2 receptors induces an intracytoplasmic calcium influx, which opens endothelial KCa channels. The resulting hyperpolarization produces vessel relaxation. During ischemic episodes, this hyperpolarization prevents intracellular calcium overload, thereby affording cardiac and microvascular protection.

Acetylcholine

Acetylcholine (ACh) is an important mediator involved in ischemic preconditioning. ACh receptors once stimulated lead to the activation of P13-K via Gi-coupling, leading to phosphorylation of Akt [44]. However, there is cross-communication between GiPCRs and EGFR, before the latter activates P13 kinase. It has been demonstrated that stimulation of GiPCR leads to a liberation of heparin-binding epidermal growth factor-like growth factor (HB-EGF), which then activates the EGFR by binding to its ectodomain with the EGFR then forming a complex that includes both Src kinase and P13 kinase [42,45,46]. P13 kinase phosphorylates membrane phosphatidylinositol in the three positions, which leads to the activation of PDK1 and PDK2 and subsequent phosphorylation of the activation sites of Akt [44,47]. This leads to generation of nitric oxide (NO), activation of PKG and opening of mitochondrial KATP channels [48]. It activated the PK resulting cardioprotection [44,49]. These results indicate that ACh (whether endogenous or exogenous) can play an important role in affording cardioprotection.

Nitric oxide

Nitric oxide plays an important role in preconditioning-induced cardioprotection. It is well noted that NO plays a prominent role both in triggering and mediating classic preconditioning. The brief episode of ischemia/reperfusion causes increased production of NO via nitric oxide synthase (NOS). This in turn activates protein kinase C, tyrosine kinase and nuclear factor kB (NF-kB) via cyclic guanosine monophosphate (cGMP)-dependent signaling pathways [49,50]. It has been noted that exogenous NO triggers the preconditioning effects which leads to opening of mitochondrial KATP channels for cell protection [51]. However, NO has also been shown to attenuate ischemic reperfusion injury by regulating myocardial cellular levels by cyclic guanosine monophosphate (cGMP) [52].

Protein kinases C

It has been demonstrated Ping et al. that PKC activation during ischemic preconditioning inhibits the mPTP [53]. PKC3 isoform increasing the activity of cytochrome C oxidase and protects the cell by decreasing ROS activity. Moreover the PKC3 also interacts with Akt and enhanced the activation of Akt and eNOS which are excellent signal for cell protection [54,55,56]. Another mitochondrial target for PKC3 is Bcl-2 associated death domain protein (BAD). It plays an anti-apoptotic role under some conditions by inhibition of BAD [57].

Protein kinase A

Calpain is a group of Ca^{2+} dependent proteases which are involved in hydrolysis of structural proteins, namely, Alfa-fodrin during reperfusion. This reduction in calpain therefore results in a decrease in the breakdown of membrane

protein cytoskeleton and sarcolemmal fragility, and hence a protection against apoptosis. Exact role of Protein Kinase A (PKA) in preconditioning remains unclear, it has been shown that cAMP and PKA levels increase after ischemic preconditioning which causes inhibition of calpain. The protective effect of PKA is blunted by beta-adrenergic blockade and pharmacologically facilitated by beta agonists. It is reported in other systems that the repeated ischemic preconditioning might lead to cAMP accumulation and direct PKA activation independently of the beta adreno-receptor through the inhibition of phosphodiesterase [58]. Finally, Manganello et al. demonstrated that PKA leading to inactivation of RhoA which directly relaxes vascular smooth muscle and increases regional myocardial blood flow [59,60]. Rho and Rho kinase inhibition have also been reported to activate endothelial NO synthase, KATP channels and attenuate production of ROS, all of which have been reported to protect the myocardial against ischemia–reperfusion injury.

Hypoxia-inducible factor

Hypoxia-inducible factor (HIF) is the principal transcription factor involved in the regulation of transcriptional responses to hypoxia. During hypoxia, HIF-a accumulates and triggers an increase in expression of genes involved in glycolysis, glucose metabolism, mitochondrial function, cell survival, apoptosis, and resistance to oxidative stress [61]. It has been noted that HIF is involved to activate the iNOS leads to cell protection [62].

The ATP-sensitive potassium channels

The ATP-sensitive potassium (KATP) channels belong to the ATP-binding cassette transporter superfamily and are comprised of two subunits: (1) a pore-forming, inward- rectifying potassium channel subunit (Kir), and (2) a regulatory sulfonylurea receptor (SUR). Both Kir and SUR subunits are required to form fully functional channels with the SUR subunit cooperating with the Kir subunit to act as ATP-dependent potassium channel complex [63]. Two ATP-sensitive potassium (KATP) channel subtypes coexist in the myocardium, with one subtype located in the sarcolemma (sarcKATP) membrane and the other in the inner membrane of the mitochondria (mitoKATP) [64-67]. Mitochondrial ATP-sensitive K+ channels (mitoKATP) have been extensively shown to participate in ischemic preconditioning [68–72]. It has been demonstrated that the effect of ischemic preconditioning mimic by mitoKATP agonists and its antagonists abrogate the protective effects of ischemic preconditioning [68,70,71,72,73,74,75]. The cardio protective results of opening mitoKATP channels include improved energy metabolism, decreased mitochondrial Ca2+ uptake during ischemia, and prevention of oxidative stress during reperfusion [76-79]. Moreover the agonist of mitoKATP channels down regulated the ROS and affords radioprotection. Reactive nitrogen species such as nitric oxide, possibly generated by mitochondria, have also been recently implicated in ischemic preconditioning [73,80]. The main effect of increased reactive nitrogen and oxygen species release during IP is to prevent oxidative stress during reperfusion [80,81]. We found that mitoKATP activation significantly decreases ROS release from isolated mitochondria. [82]. The role of mito K-ATP in protecting against apoptosis, several recent studies showed that diazoxide pretreatment decreases the appearance of apoptotic markers resulting from ischemia/reperfusion injury [83]. Recent study showed that ischemic preconditioning blunted the up-regulation of Bax protein expression associated with ischemia/reperfusion without altering the levels of Bcl-2 leads to control the apoptosis [84].

Mitochondrial Permeability Transition Pore

Mitochondrial Permeability Transition Pore (mPTP) is playing an important role in cardiovascular complications. Inhibition of mPTP opening is responsible for cardioprotection [85]. However nitric oxide also prevents mPTP opening [86]. It is noted that the mPTP is inhibited with the activation of mKATP channels [87]. In general, it is thought that the opening of the mPTP occurs with a decrease in the inner matrix potential, decreased AMP and ADP levels, and increased matrix Ca^{2+} results oxidative stress [88]. The mPTP opening increases osmotic forces within the mitochondria inner matrix and leads to degradation of the matrix membrane, causing the release of apoptotic factors, especially cytochrome C [89].

JAK-STAT Pathway

The involvement of JAK-STAT pathway in conferring cardioprotection has been demonstrated in both early and late preconditioning [90,91]. The expression of stress-responsive genes is the Janus tyrosine kinase (JAK)–signal transducers and activators of transcription (STAT) signaling pathway that involves two families of proteins, JAKs and STATs, which transduce extracellular signals into the nucleus resulting in transcriptional activation of target genes. Four JAKs have been identified (JAK1, JAK2, JAK3, and TYK2), all of which are activated by tyrosine phosphorylation. Activation of STATs requires phosphorylation of tyrosine residues in the Src homology 2 domain. Once they are phosphorylated by JAKs, STAT proteins homodimerize or heterodimerize and translocate to the

nucleus, where they transactivate STAT-responsive genes [92–95]. JAK/STAT pathway mediates cardioprotection afforded by IPC through attenuation of apoptotic cell death during reperfusion [96-97].

CONCLUSION

The cardioprotective potential of myocardial preconditioning has been well evidenced in clinical conditions. However, numerous experimental and clinical studies revealed that the infarct size-limiting effect of preconditioning was blunted in various pathological conditions such as hypercholesterolemia, hyperglycemia, hypertension, cardiac hypertrophy, aging, obesity and hyperhomocysteinemia. Number of studies demonstrated the cardioprotective potentials of ischemic preconditioning. These potentials of ischemic preconditioning are evidenced by the implication of cardioprotective pathways including cell surface receptors, adenosine, bradykinin, nitric oxide, acetylcholine, protein kinases, mPTP and mito KATP channels. Therefore, these pharmacological agents have been shown to mimic the cardioprotective effects of ischemic preconditioning. The infusion of these agents in patients with ischemic heart disease undergoing surgery could improve the outcome of myocardial function by reducing I/R-induced myocardial injury.

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