REVIEW ARTICLE

Ischemic preconditioning: Interruption of various disorders

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Ischemic heart diseases are the leading cause of morbidity and mortality worldwide. Reperfusion of an ischemic heart is necessary to regain the normal functioning of the heart. However, abrupt reperfusion of an ischemic heart elicits a cascade of adverse events that leads to injury of the myocardium, i.e., ischemia–reperfusion injury. An endogenous powerful strategy to protect the ischemic heart is ischemic preconditioning, in which the myocardium is subjected to short periods of sublethal ischemia and reperfusion before the prolonged ischemic insult. However, it should be noted that the cardioprotective effect of preconditioning is attenuated in some pathological conditions. The aim of this article is to review present knowledge on how menopause and some metabolic disorders such as diabetes and hyperlipidemia affect myocardial ischemic preconditioning and the mechanisms involved.

Keywords: Diabetes, Hyperlipidemia, Ischemic preconditioning, Menopause

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Abbreviations

I/R	ischemia/reperfusion
IPC	ischemic preconditioing
ROS/RNS	reactive oxygen or nitrogen species
PI3K	phosphatidylinositol 3-kinase
PIP3	phosphatidyl-inositol 3,4,5-triphosphate
PIP2	phosphatidyl inositol 3,4-biphosphate
PDK	phosphoinositide-dependent kinase
Akt	protein kinase B
PKC	protein kinase C
GSK3β	glycogen synthase kinase-3β
NO	nitric oxide
mitoK$_{ATP}$	mitochondrial ATP-sensitive potassium channels
DAG	diacylglycerol
IP3	inositol triphosphate
ROS	reactive oxygen species
MAPK	mitogen activated protein kinases
ERK	extracellular signal-regulated kinases
mPTP	mitochondrial permeability transition pore
ATP	adenosine triphosphate
eNOS	endothelial nitric oxide synthase
RISK	reperfusion injury salvage kinase
GSH	glutathione
*i*NOS	inducible nitric oxide synthase
MMP	matrix metalloproteinases
STZ	streptozotocin
TNF	tumour necrosis factor
NADPH	nicotinamide adenine dinucleotide phosphate
ER	estrogen receptor
AR	adrenergic receptor

Introduction

Coronary heart disease is a leading and growing problem in most of the developing regions of the world and the most common mode of cardiovascular death is ischemic heart disease and stroke [1]. Myocardial ischemia occurs when there is insufficient blood supply to the myocardium [2]. Although early reperfusion protects the myocardium from damage, reperfusion after a prolonged ischemic insult causes tissue injury, i.e., ischemia–reperfusion (I/R) injury [3,4]. It is characterized by a cascade of adverse events—local inflammatory responses, metabolic disorder, and cell death—leading to myocardial ultrastructural changes and subsequently myocardial systolic and diastolic dysfunction [5–7]. Some experimental studies suggest that reactive oxygen species (ROS) or reactive nitrogen species, including superoxide radicals, hydrogen peroxide, hydroxyl radicals, singlet oxygen and peroxynitrite ($ONOO^-$) are mainly responsible for myocardial I/R injury [8,9].

Ischemic preconditioning and its molecular mechanism

The strategy to prevent I/R injury was given by Murry and coworkers [10] in 1986. They showed that brief intermittent periods of sublethal ischemia followed by reperfusion have a protective effect on myocardial tissue against prolonged ischemic insult; this is called ischemic preconditioning (IPC) [10,11]. IPC is found to be a biphasic phenomenon: an early phase that starts within minutes and wanes off gradually within 2–3 hours, called classical preconditioning [12,13]; and the late phase, which is delayed to 12–24 hours after the ischemic stress and lasts up to 3–4 days, and is called late-phase preconditioning or second window of protection [14,15]. The early phase of IPC protects only against the myocardial infarction but the late-phase IPC also protects against myocardial stunning [16,17].

Preconditioning results in 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 initiate 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 from cell membrane lipid phosphatidyl inositol 3,4-biphosphate leading to activation of phosphoinositide-dependent kinase 1 (PDK1) and subsequent activation of protein kinase B (Akt) and p70S6-kinase [27,28]. PI3K/Akt activation upregulates protein kinase C (PKC) [29], phosphorylation of glycogen synthase kinase-3β (GSK3β) [30], generation of nitric oxide (NO) [29], and activates the mitochondrial adenosine triphosphate-sensitive potassium channels (mitoK$_{ATP}$) [31,32].

The activated phospholipase C leads to generation of two second messengers (diacylglycerol and inositol triphosphate) by hydrolysis of phosphatidyl inositol 3,4-biphosphate. Diacylglycerol activates protein kinase C by translocating it from cytosol to the perinuclear membrane [33,34]. PKC activation has been shown to be important in the opening of mitoK$_{ATP}$ [35]. PKC$_\varepsilon$ and PKC$_\delta$ have 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 ROS [37]. ROS generation

during preconditioning also activates PKC [38,39]. Although a large burst of ROS leads to cell damage, a moderate release during nonlethal short episodes of ischemia plays a significant triggering role in the signal transduction pathways of IPC [40]. PKC$_\varepsilon$ also forms a complex with mitochondrial permeability transition pore (mPTP) [41,42], which leads to a decrease in the release of cytochrome C and apoptotic cell death [43,44]. In addition, IPC also activates extracellular signal-regulated kinase (ERK)1/2 during the preconditioning phase as well as the reperfusion phase, which mediates the inhibition of mPTP opening through various mechanisms [45].

More recent interest has focused on GSK-3β, phosphorylated (and hence inactivated) by other kinases, including Akt and p42/p44 ERK1/2 mitogen activated protein kinase [30,46]. GSK-3β plays a crucial role in apoptosis and necrosis of cardiomyocytes [47]. Experimental studies have reported that GSK-3β confers cardioprotective effects through its potential mitochondrial effects including inhibition of mPTPs opening and control of mitochondrial adenine nucleotide transport through the outer mitochondrial membrane [48–50].

Although IPC provides a remarkable cardioprotection, its effectiveness is attenuated in animal models of some diseases, including hyperlipidemia, diabetes, nitrate tolerance, heart failure, menopause in women, and aging due to alteration in intracellular signaling relevant to cytoprotection and thus myocardial responses to IPC [51,52].

Methods

Relevant studies were identified through electronic searches of Pubmed, Medline, Scopus, and Google scholar. The search used the terms ‘‘ischemia reperfusion,’’ ‘‘ischemia reperfusion injury,’’ or ‘‘ischemic preconditioning,’’ paired with ‘‘diabetes mellitus,’’ ‘‘hyperlipidemia,’’ ‘‘hy percholesterolemia,’’ ‘‘postmenopause,’’ and ‘‘ov ariectomized,’’. In addition, we searched the bibliographies of relevant studies, reviews, and editorial letters between 1983 and 2016 for articles in English.

Diabetes mellitus

Diabetes mellitus is a disorder of carbohydrate, protein, and lipid metabolism affecting many organs, which ultimately leads to severe acute and chronic complications [53]. Hyperglycemia has been reported to impair coronary microvascular responses to ischemia [54], reduces the availability of nitric oxide [55], and enhances the oxygen derived free radical production [56].

I/R injury in the diabetic heart

Ischemic heart disease is significantly more common and severe in patients with diabetes than in nondiabetics [57]. However, it is unclear whether resistance to ischemia is greater or lower in diabetic hearts [58,59]. Moreover, in patients with diabetes, the mortality rate after an acute myocardial infarction or coronary bypass surgery is almost double that of nondiabetics [60].

Insulin modulates the glucose transport, glycogen synthesis, glycolysis, protein synthesis, lipid metabolism, growth, contractility, and apoptosis in cardiomyocytes. Thus the reduction of these insulin-stimulated effects may be responsible for the increased myocardial injury during ischemia and reperfusion in diabetic patients [61,62]. Diabetes mellitus also disturbs the function of cardiac subcellular organelles, including the sarcolemma, sarcoplasmic reticulum, and mitochondria [63]. The lower glycolytic rates and impaired oxidation result in loss of ATP [64], altered expression of adenosine receptors [65], and impairment of K_{ATP} channels [66], which worsen the I/R induced myocardial injury.

In contrast, some experimental studies showed that the diabetic heart is resistant to I/R injury [67–69], which may be due to elevated antioxidant defenses [70,71], depressed sarcoplasmic reticulum calcium pump activities [72], depressed sodium–calcium exchange [73], decreased sensitivity of β-adrenergic stimulation [74,75], upregulation of PKC [76], and release of protective calcitonin gene related peptide [77].

Impact of diabetes on IPC and mechanisms involved

It has been documented that IPC-induced cardioprotection is attenuated or eliminated in rats with spontaneous Type 2 diabetes [78] and the myocardium from patients with diabetes cannot be protected by preconditioning [79]. Unfortunately, however, research on whether the diabetic myocardium can be protected by IPC is in conflict [80]; some studies have reported that diabetic hearts can be protected by IPC [81,82], and the majority have reported fewer or no protective effects [82–84].

It has been suggested that K_{ATP} channels in the myocytes of streptozotocin-induced diabetic rats open at higher intracellular ATP levels than do K_{ATP} channels in normal control rats [85], which

may be one hurdle in IPC-induced cardioprotection in the diabetic heart. One reason of failure to precondition the diabetic myocardium that has been also reported is dysfunction in mitochondrial superoxide production [86], which is an important element of the signal transduction pathway of preconditioning [87]. Diabetes also alters the function of vascular and myocardial K_{ATP} channels [85,88]. In addition to this, channel density also appears to be diminished in diabetic hearts [89], and this may be one reason for IPC not developing in diabetic hearts.

It has been observed in that attenuation of the cardioprotective effect of IPC in diabetic rat heart is due to some defect in the caveolin–endothelial nitric oxide synthase (eNOS) complex in diabetic heart, which leads to a decrease in the availability of NO and the consequent decreased activation of mitoK_{ATP} channels [90]. Moreover, the loss of preconditioning is also observed in the presence of sulfonylurea drugs [91,92], and the mechanism of this has been found to be inhibition of K_{ATP} channels present in both pancreatic β cells [93] and cardiac myocytes [94].

Tsang and coworkers [95] for the first time reported that the Type2 diabetic myocardium can be protected by IPC, but the threshold required to achieve this protection is greater than that required for nondiabetic hearts, and this elevated threshold is required to achieve sufficient phosphorylation of Akt to execute the IPC protective signal. By contrast, Tatsumi and coworkers [81] found less cumulative creatine kinase release in preconditioned diabetic hearts than in normal hearts, and thus concluded that, in the diabetic myocardium, preconditioning may offer greater protection than in the normal myocardium. Further, hyperglycemia may lead to upregulation of endogenous stress protein, i.e., hsp-27 in Type 1 diabetic mice, which has a potential role in cardioprotection and compensates for detrimental effects of hyperglycemia [96].

However, whether diabetes eliminates IPC mediated myocardial protection depends on IPC times or the periods of diabetes. For instance, Ting and co-workers [97] showed that mice with diabetes for 4 weeks showed tolerance to I/R induced damage comparable to normal rats and partial IPC-induced myocardial protection, while mice with diabetes for 8 weeks showed low tolerance to I/R-induced damage compared to normal rats and no evidence of IPC induced myocardial protection. In another study on streptozotocin-induced diabetic rat heart, it was reported that the 2-week diabetic heart was resistant to I/R injury, but the protection was not shown in 4-week and 6-week diabetic hearts, and there is a worse outcome of I/R in 8-week diabetic hearts [84].

Furthermore, it has been demonstrated that diabetes-induced activation of GSK-3β and impairment of the reperfusion injury salvage kinase pathway play important roles in diabetes-induced myocardial oxidative damage [98]. It is well known that IPC produces myocardial protection by phosphorylation and thus inactivation of GSK-3β that inhibits the opening of mPTP, but the activity of GSK-3β was found to be elevated during diabetes [99,47,100]. In our laboratory, Yadav and coworkers [101] investigated the role of GSK-3β in attenuating the cardioprotective effect of IPC using a Type-1 diabetic rat model and found that the cardioprotective effect of IPC was significantly attenuated in diabetic rats compared to normal rats. At the same time, they found that GSK-3β inhibitors, including lithium chloride, indirubin-3 monooxime, and SB216763, significantly reduced the myocardial damage and decreased infarct size in diabetic rat myocardium. This study suggests that diabetes-induced attenuation of myocardial protection mediated by IPC involves the activation of GSK-3β.

Emerging evidence indicates that IPC-mediated myocardial protection is predominantly mediated by stimulating PI3K/Akt and the associated GSK-3β pathway while diabetes-mediated pathogenic effects are found to be mediated by inhibiting this pathway. Therefore, we may activate PI3K/Akt indirectly to inactivate the GSK-3β pathway or use the GSK-3β inactivator directly to inactivate the GSK-3β pathway to preserve IPC-mediated myocardial protection under diabetic conditions. However, further studies are required to observe the involvement of proposed mechanisms in attenuation of IPC-mediated myocardial protection in hyperglycemic patients. The possible mechanisms involved in hyperglycemia-induced attenuation of cardioprotective effect of IPC are shown in Fig. 1.

Hyperlipidemia/hypercholesterolemia

Hyperlipidemia is a well-known risk factor in development of cardiovascular diseases, as it contributes to the formation of atherosclerotic plaques in coronary vessel [102]. Although many of the studies have shown that hyperlipidemia attenuates the IPC-induced cardioprotection, there is a controversy as to whether hyperlipidemia

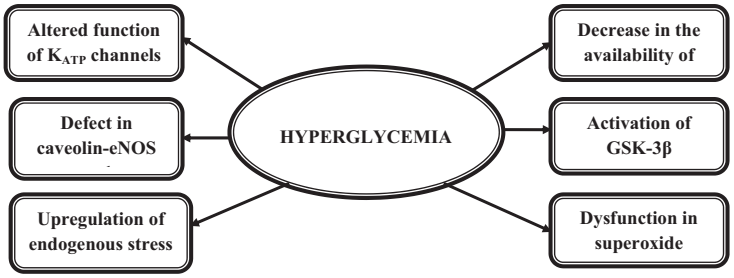

Fig. 1. Mechanisms involved in hyperglycemia induced attenuation of cardioprotective effect of preconditioning. eNOS = endothelial nitric oxide synthase; GSK3β = glycogen synthase kinase-3β; K_{ATP} = adenosine triphosphate-sensitive potassium channels; NO = nitric oxide.

interferes with the infarct size-limiting effect of preconditioning [52]. This may be attributed to differences in hyperlipidemia models (species, duration of hyperlipidemic diet, presence of significant coronary sclerosis).

I/R injury in hyperlipidemic heart

Some experimental studies have reported that hypercholesterolemia increases the myocardial infarct size in rabbits subjected to I/R after exposure to short-term (2–3 weeks) cholesterol diet compared to rabbits fed a long-term (5–16 weeks) cholesterol diet or a normal diet [103]. Golino and coworkers [104] reported that the myocardial infarct size was dramatically increased in rabbits subjected to ischemia and reperfusion after only a 3-day cholesterol diet. In mice, however, short-term high cholesterol diet does not influence the infarct size in wild-type animals, although it markedly increases the infarct size in low-density lipoprotein receptor deficient animals [105]. However, long-term (>6 weeks) high cholesterol diet protects the myocardium from I/R injury in rabbits [106] and in wild-type and low-density lipoprotein receptor deficient mice [105]. These opposing findings may be attributed to reduction of myocardial glutathione levels after a 2-week cholesterol diet but increased glutathione levels after 12 weeks [105]. It has also been reported that hyperlipidemia prevents the normal reduction of myocardial ischemia on repeated balloon inflations during angioplasty in humans [107].

Impact of hyperlipidemia on ischemic preconditioning and mechanisms involved

Hypercholesterolemia, irrespective of the development of atherosclerosis, interferes with the cardioprotective mechanisms of IPC [108]. This loss of preconditioning was further confirmed in isolated hearts of rat with chronic exposure to cholesterol diet [109]. It has been well documented by means of a beat-to-beat analysis of ST segments that hypercholesterolemia attenuates the IPC-induced anti-ischemic effect, accelerates the evolution of myocardial ischemia, and delays the reperfusion recovery from ischemia in humans [110].

Researchers were able to induce late preconditioning in hyperlipidemic rabbits only when the numbers of IPC cycles was increased compared to that applied in normolipidemic rats to induce late preconditioning [111], which suggests that the threshold to trigger cardioprotection is increased in experimental hyperlipidema. Hypercholesterolemia abrogates the late preconditioning, possibly by preventing upregulation of tetrahydrobiopterin synthesis, an essential cofactor for inducible NO synthase [112].

Hypercholesterolemia causes oxidative/nitrosative stress leading to myocardial dysfunction [113]. It has been observed that the reduced NO release from rabbit aorta in hypercholesterolemia [114] and the high cholesterol concentrations in endothelial cell membranes caused downregulation of NO synthase [115]. Reduced vascular NO release in hyperlipidemia has been also shown as a consequence of increased release of superoxide, which then reacts with NO to form $ONOO^-$ [116,117].

It has been established that cholesterol-enriched diet-induced hyperlipidemia leads to increase in cardiac $ONOO^-$ formation and a decrease in the NO bioavailability which leads to the deterioration of cardiac performance and further cardiac pathologies [118]. This peroxynitrite is also responsible for rapidly increasing the release of a large family of zinc endopeptidases, matrix metalloproteinases (MMPs) in coronary effluent via a nonproteolytic oxidative mechanism resulting in fully active proenzymes [119,120]. Moreover, hyperlipidemia has been shown to diminish IPC-induced inhibition of myocardial MMP-2 activation and release in to the coronary perfusate [121]. This MMP-2 promotes vasoconstriction in rat mesenteric arteries [122], and

ischemia-induced activation and release of MMP-2 contributes to acute mechanical dysfunction after I/R in rat hearts [123,124].

One study suggested that in hyperlipidemia, there is an alteration in one of the main signal transduction elements, i.e., distribution of the intracellular localization of Connexin 43 in the heart that takes part in gap junction formation and thus in electrical and chemical coupling of cardiomyocytes, and in that study the protective effect of preconditioning was found to be lost in hyperlipidemia [125]. In addition, hyperlipidemia has been shown to suppress the opening of mitoK_{ATP} channels in the rabbit heart subjected to I/R [126].

The antihyperlipidemic drugs, statins increase the half-life of NO synthase mRNA in human saphenous vein endothelial cells [127], increase PI3K activity in cultured human umbilical vein endothelial cells and bovine aortic endothelial cells [128] and adenosine production in SV40-transfected aortic rat endothelial cells [129], showing the cardioprotective effect independently of cholesterol-lowering effects. Thus, it seems a possible explanation that cholesterol-enriched diet-induced hypercholesterolemia increases nicotinamide adenine dinucleotide phosphate oxidase and cardiac superoxide, thereby leading to increased peroxynitrite production, resulting in activation of MMPs that ultimately leads to cardiac dysfunction. Thus lowering of serum cholesterol, targeting $ONOO^-$ with pharmacological tools, and pharmacological inhibition of MMP-2 may be new strategies to protect the heart and the vasculature in hyperlipidemia. Taken together, further studies are requisite to elucidate the interference of hyperlipidemia with the infarct size-limiting effect of preconditioning. Possible mechanisms involved in hyperlipidemia induced attenuation of cardioprotective effect of preconditioning are shown in Fig. 2.

Postmenopause

The incidence of coronary heart disease is relatively low among premenopausal women and increases sharply with the occurrence of menopause [130], which indicates that the female sex hormones, particularly estrogen, play a crucial role in reducing the risk of ischemic heart diseases [131,132]. Although animal models with surgical menopause (ovariectomy) indicate the cardioprotective effect of estrogen replacement [133,134], some clinical trials failed to demonstrate any cardioprotection from such estrogen replacement therapy [135,136]. In fact, the incidence of ischemic

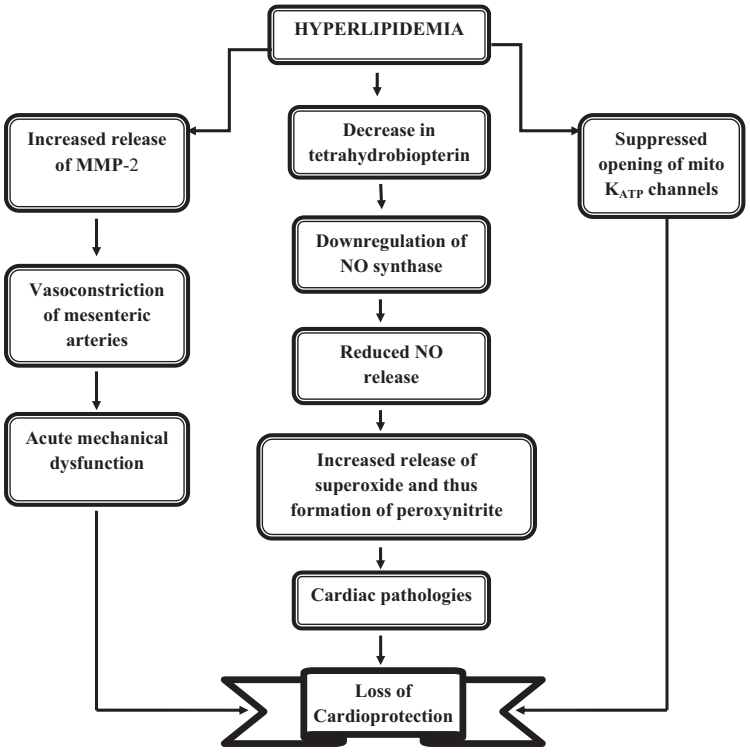

Fig. 2. Mechanisms involved in hyperlipidemia induced attenuation of cardioprotective effect of preconditioning. mitoK_{ATP} = mitochondrial adenosine triphosphate-sensitive potassium channels; MMP = matrix metalloproteinases; NO = nitric oxide.

heart disease was increased in women receiving estrogen compared to those receiving placebo [136].

I/R injury in postmenopausal heart

Cardiomyocytes from female hearts are more resistant to I/R injury than those from male hearts [137]. There are sex differences in the myocardial response to acute I/R injury, and the increased phosphorylated Akt and phosphorylated PKCε levels in female hearts are responsible for these sex-related differences in heart susceptibility to I/R and play an important role in cardioprotection against I/R injury in female hearts [138].

Cardiac myocytes and some other cardiac cells produce tumor necrosis factor (TNF)-α [139], and the increased TNF-α levels after an ischemic event contribute to myocardial injury [140]. Estrogen deficiency and menopause are associated with increased TNF-α levels, which may lead to increased myocardial injury after menopause [141]. In another study, it is reported that decreased mitochondrial respiration and increased mPTP opening with aging are responsible for necrotic cell death associated with I/R injury in aged female rats [142].

Impact of menopause on ischemic preconditioning and mechanisms involved

Shinmura and coworkers [143] demonstrated that the cardioprotective effect of IPC is lost in ovariectomized (surgical menopause) rats, which is partly due to impaired translocation of PKCε to the membranous fraction and phosphorylation of PKCε and PDK1. However, estrogen replacement or selective activation of PKCε-mediated signaling can fully restore the IPC effect, the translocation and phosphorylation of PKCε, and the phosphorylation of PDK1 [143]. It has been well documented by our laboratory that ovariectomy reduces the activity of eNOS in cardiac tissue due to upregulation of its inhibitory protein caveolin [144], but the chronic estrogen treatment accompanies restoration of normal activity of myocardial eNOS [145].

Endogenous and exogenous estrogen in pre- and postmenopausal women, respectively, protects against the cardiovascular disease [146,147]. Estrogen acts as a vasoprotective molecule by increasing bioavailability of NO [148,149]. Estrogen upregulates eNOS and downregulates its inhibitory protein, caveolin-1 [150,151]. The effect of estrogen on eNOS expression is mediated via estrogen receptor (ER)α and ERβ, which are present on endothelial cells [152]. Activation of eNOS by estrogen has been reported to occur through the ERK-1/2 [153] pathway as well as via the PI3K/Akt pathway [154–156]. The recruitment of the latter cascade depends on the ligand dependent association of ERα with PI3K [154]. Akt can be activated by estrogen [157], which further activates eNOS by phosphorylating it at serine 1177 residue [158,159]. This phosphorylation not only activates eNOS but also increases the efficiency of activation by Ca^{++}/calmodulin [160]. Thus estrogen increases the bioavailability of NO and thus results in decrease in myocardial injury. In addition, 17β-estradiol has been shown to reduce myocardial necrosis in rabbits after I/R [161] and improve recovery of mechanical function following global ischemia in isolated rat hearts [162,163]. The cardioprotective effects of estrogen are in part mediated by regulation of TNFα levels in the ischemic heart [164].

It has been found that the development of cardiovascular diseases after menopause is not only due to the decrease in estrogen but also due to the decrease in androgen [165]. Furthermore, it has been reported that testosterone enhances

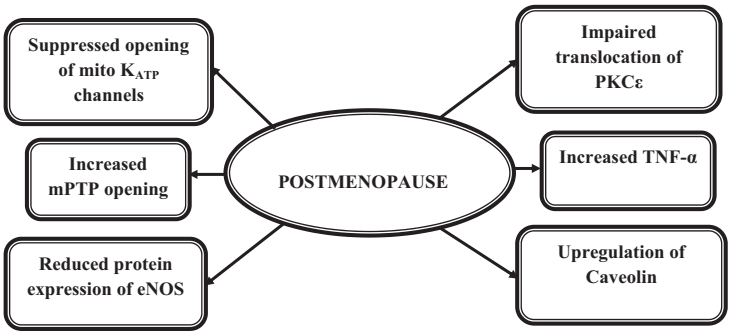

Fig. 3. Mechanisms involved in menopause-induced attenuation of cardioprotective effect of preconditioning. eNOS = endothelial nitric oxide synthase; mitoK_{ATP} = mitochondrial adenosine triphosphate-sensitive potassium channels; mPTP = mitochondrial permeability transition pore; PKC = protein kinase C; TNF = tumor necrosis factor.

estradiol's cardioprotection in ovariectomized rats, estradiol and testosterone combination protects cardiomyocytes against I/R injury, and the protective effects are at least partly mediated by β2-adrenergic receptor [166]. These findings illustrate the need for better understanding of changes contributing to impaired ischemic tolerance in the postmenopausal heart and for finding the alternative therapeutics to reduce injury during myocardial infarction in postmenopausal women. The possible mechanisms involved in menopause-induced attenuation of the cardioprotective effect of IPC are shown in Fig. 3.

Conclusion

The cardioprotective potential of IPC is well established, but it is lost in various clinical conditions such as hyperglycemia, hypercholesterolemia, and menopause. In these conditions the outcome of I/R injury worsens and the infarct size-limiting effect of IPC is blunted. This may affect the clinical application of IPC in patients undergoing cardiac surgery who also have the above mentioned clinical conditions. Therefore, there is a need to explore the underlying mechanisms of altered IPC-induced cardioprotection in various clinical conditions in order to identify the rational approaches for the protection of hyperglycemic, hyperlipidemic, and post-menopausal heart.

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