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REVIEW

Diabetes abolish cardioprotective effects of remote ischemic conditioning: evidences and possible mechanisms

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Abstract

Diabetes mellitus significantly hampers the development of cardioprotective response to remote pre/post/perconditioning stimuli by impairing the activation of cardioprotective signaling pathways. Among the different pathways, the impairment in O-linked β-*N*-acetylglucosamine (O-GlcNAc) signaling and release of cardioprotective humoral factor may contribute in attenuating remote preconditioning-induced cardioprotection. Moreover, the failure to phosphorylate extracellular signal related kinase (ERK), phosphoinositide-3-kinase (PI3K), and AKT along with up-regulation of mechanistic target of rapamycin (mTOR) and decrease in autophagy may also attenuate remote preconditioning-induced cardioprotection. Remote perconditioning stimulus also fails to phosphorylate AKT kinase in diabetic heart. In addition, diabetes may increase the oxidative stress, reactive oxygen species (ROS) production, decrease the beclin expression, and inhibit autophagy to attenuate remote perconditioning-induced cardioprotection. Moreover, diabetes-induced increase in the Rho-associated kinase (ROCK) activity, decrease in the arginase activity, and reduction in nitric oxide (NO) bioavailability may also contribute in decreasing remote perconditioning-induced cardioprotection. Diabetes may reduce the phosphorylation of adenosine 5′-monophosphate activated protein kinase (AMPKα) and increase the phosphorylation of mTOR to attenuate cardioprotection of remote postconditioning. The present review describes the role of diabetes in attenuating remote ischemic conditioning-induced cardioprotection along with the possible mechanisms.

Keywords Oxidative stress · Heart · Diabetes · Autophagy · ROCK

Introduction

Remote ischemic conditioning (RIC) is the phenomenon in which short, repeated cycles of ischemia and reperfusion to a remote organ (other than heart) confer protection to heart against sustained ischemia–reperfusion injury [43, 54]. Indeed, in this treatment approach, there is activation of an endogenous protective adaptive response in the heart for counteracting ischemia–reperfusion injury [46, 50]. On the basis of time of delivery (before, during, or after sustained ischemia) and site of delivery (type of remote organ) of conditioning stimulus, remote ischemic conditioning is classified into different types. In remote ischemic preconditioning, short cycles of ischemia and reperfusion are delivered to the remote organ before index ischemia (sustained ischemia) [15]. In remote ischemic perconditioning, conditioning stimulus is delivered to the remote organ during the time of sustained cardiac ischemia. In remote ischemic post-conditioning, short cycles of ischemia and reperfusion are delivered to the remote organ during the initial minutes of heart reperfusion [10, 69]. Apart from the time of delivery, remote ischemic conditioning has also been classified into different types depending on the remote organ, which is subjected to short episodes of ischemia and reperfusion. In remote iliac artery ischemic conditioning, conditioning stimulus is delivered by clamping the iliac artery [41]. In remote renal conditioning, remote mesenteric conditioning, and remote hind limb conditioning, the conditioning stimulus is delivered by occluding renal arteries, mesenteric arteries, and femoral arteries, respectively [5, 6, 12, 15, 47–49, 55, 68]. Among these, remote hind limb conditioning has also been employed in the clinical studies because

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N.S. helped in literature review and completion of the article
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the hind limb may be occluded non-invasively by tying one of the limbs with the blood pressure cuff [7, 26, 32].

There have been a large number of studies documenting the clinical efficacy of remote ischemic conditioning in patients undergoing heart surgery [56, 60]. Moreover, this phenomenon is also shown to improve coronary artery function in patients with stable coronary artery disease [9]. On the other hand, some meta-analysis studies have documented that remote ischemic conditioning is unable to yield promising results in various cardiovascular disease conditions [19, 22, 40]. The lack of cardioprotective effects of remote conditioning in these clinical trials may be possibly attributed to certain factors that may limit its clinical application in patients [61]. Indeed, there have been studies showing that the beneficial effects of remote ischemic conditioning in humans is influenced by various factors including aging [33, 42, 51], comorbidities such as angina pectoris, hypertension, hyperlipidemia, heart failure, cardiac hypertrophy, changes in the coronary artery circulation, insulin resistance, and diabetes mellitus [13, 39, 63]. The pharmacotherapy used for treating these comorbidities or for other purposes such as statins, nitrates, oral hypoglycemic agents [8, 37], and anesthetics [30] may also affect the cardioprotective ability of remote ischemic conditioning [13]. Diabetes mellitus poses a significant challenge to the successful implementation of ischemic conditioning in protecting hearts in clinical setting [64]. On a similar lines, there have been a number of studies demonstrating a decrease in the cardioprotective effects of remote ischemic pre/per/postconditioning during diabetic state owing to interference with the cardioprotective mechanisms, defective post receptor signaling, or/and changes in the functioning of the mitochondria [4, 16, 21, 23, 24, 27, 28, 42]. The present review describes diabetes or an increase in glucose levels as one of the major risk factors in attenuating remote ischemic conditioning-induced cardioprotection along with the possible mechanisms.

The literature search for writing this present review was done using www.Pubmed.com as the search engine and different combinations of keywords were used to search the literature. These included "remote preconditioning, diabetes and heart," "remote perconditioning, diabetes and heart," and "remote postconditioning, diabetes and heart." The cross-references from the papers collected from PubMed were also used to collect diabetes and remote conditioning-related literature.

Evidences that diabetes abolishes cardioprotective effect of remote ischemic conditioning

Remote ischemic preconditioning

There have been reports suggesting that diabetes mellitus or an increase in glucose levels may impair the cardioprotective effect of remote ischemic preconditioning. Hu et al. reported the impact of acute streptozotocin (STZ, 50 mg/kg, i.p.)-induced diabetes mellitus on left coronary artery ligation-induced ventricular arrhythmia in remote ischemic preconditioning subjected rats. Four cycles of 5 min of ischemia and 5 min of reperfusion served as remote ischemic preconditioning stimulus before myocardial ischemia reperfusion injury (5 min of ischemia followed by 20 min of reperfusion). The severity of arrhythmia was assessed by noting the development of ventricular tachycardia, fibrillation, and atrioventricular block. The authors reported that remote ischemic preconditioning significantly reduces all types of arrhythmias induced by ischemic reperfusion injury in non-diabetic rats, but it did not attenuate the incidence of all types of arrhythmias in diabetic rats. The atrioventricular block was significantly less (fourfold) in remote ischemic preconditioning-subjected rats as compared to control group of non-diabetic rats. However, remote ischemic preconditioning failed to attenuate atrioventricular block in diabetic rats [21].

A clinical study of Jensen et al. reported that remote preconditioning-induced release and effect of a circulating cardioprotective factor is reduced in type 2 diabetes mellitus patients suffering from peripheral neuropathy. Blood samples were withdrawn from nine non-diabetic patients, eight diabetic patients with no symptoms of peripheral neuropathy, and eight diabetic patients with symptoms of peripheral neuropathy before (control) and after remote ischemic preconditioning stimulus. In test persons, remote ischemic preconditioning stimulus of 4 cycles comprising 5 min of upper-arm ischemia and 5 min of reperfusion was given by inflation (up to 200 mmHg) and deflation of blood pressure cuff. After the initial 4 cycles of 5 min remote ischemic preconditioning stimulus, test persons with diabetic neuropathy immediately underwent additional 2 cycles of 10 min remote ischemic preconditioning stimulus (intensified remote ischemic preconditioning stimulus). The blood samples were withdrawn, dialyzed, and the cardioprotective effects of the dialysates were tested in rabbit hearts mounted on the Langendroff system [23]. It was reported that myocardial infarct size, the post-ischemic left ventricular developed pressure, dp/dt_{min}, dp/dt_{max} along with the rate pressure product were improved in rabbits' hearts perfused with dialysate from both non-diabetic and diabetic subjects without peripheral neuropathy receiving remote ischemic preconditioning. However, dialysate obtained from diabetic neuropathy patients subjected to remote ischemic preconditioning episodes failed to reduce infarct size and improve contractility parameters. Furthermore, dialysate from the patients subjected to intensified remote ischemic preconditioning also failed to confer cardioprotection. Therefore, it was suggested that the presence of intact neurogenic pathway is essential for the release of the cardioprotective humoral factor during remote ischemic preconditioning. Accordingly, due to non-functional neurogenic

pathway in diabetic neuropathy, the cardioprotective effect of dialysate from remote ischemic preconditioning subjected diabetic patients was not observed [23].

Another study from the same group of scientists also reported that diabetes influences the cardioprotective effects of remote preconditioning (Table 1). The effects of plasma dialysate obtained from healthy persons ($n = 8$) and type 2 diabetic patients ($n = 8$) before and after remote ischemic preconditioning stimulus were tested on human isolated atrial trabeculae against ischemia–reperfusion injury (ischemia of 30 min and reperfusion of 120 min). The dialysate obtained from normal persons after remote preconditioning produced cardioprotective effects on human atrial trabeculae. Similarly, dialysate isolated from diabetic persons produced cardioprotective effects; however, remote ischemic preconditioning stimulus in the diabetic patients failed to produce any additional beneficial effects [24].

Remote ischemic perconditioning

Apart from remote preconditioning, diabetes and acute hyperglycemia also abolish remote ischemic perconditioning-induced myocardial protection. A study of Baranyai et al. demonstrated that an acute rise in glucose levels attenuates remote ischemic perconditioning-induced cardioprotection in rats. Animals received 50% dextrose infusion to induce acute hyperglycemia and serum glucose levels were maintained at 15–20 mM concentration. In normal glycemic animals, 46% mannitol infusion was administered to maintain the similar osmolarity. Remote perconditioning stimulus was delivered by alternatively tying and untying the femoral vessels (arteries and veins) for short periods [4]. The study reported that remote ischemic perconditioning significantly reduces the extent of infarction in normoglycemic animals, while it does not decrease the infarct size in acute hyperglycemic animals. The authors also documented that the acute rise in glucose levels did not modulate ischemia-induced myocardial injury. This report is in contrast to studies showing that acute hyperglycemia per se increases the extent of infarction [25, 58]. These contradictory reports may be possibly due to the different glucose concentrations employed in these studies. The reports suggesting an enhancement in infarction in ischemia-subjected animals have employed relatively higher concentration of glucose (more than 30 mM concentration) [38]. On the contrary, Baranyai et al. maintained much lower concentration of glucose, i.e., 15–20 mM and documented no per se influence of acute hyperglycemia on ischemic injury. In contrast, the authors documented that the incidence and duration of arrhythmias was higher in acute hyperglycemic animals in comparison to normoglycemic animals during ischemic period. Moreover, remote ischemic perconditioning did not modulate arrhythmia in hyperglycemic and normoglycemic animals [4].

A study of Kiss et al. reported that remote ischemic perconditioning significantly reduces the myocardial infarct area in non-diabetic rats, but fails to modulate infarction in type 1 diabetic rats. However, the degree of myocardial infarction was comparable in non-diabetic and diabetic rats in response to ischemia–reperfusion injury. Remote ischemic perconditioning stimulus was delivered by occluding bilateral femoral arteries for 15 min during myocardial ischemia (30 min of coronary artery ligation followed by 2 h of reperfusion) [27, 28].

Remote ischemic postconditioning

A study of Han et al. demonstrated that autophagy plays a critical role in inducing cardioprotective effects of remote ischemic postconditioning in response to ischemia–reperfusion injury in normal mice, but not in diabetic mice. A single dose of STZ (150 mg/kg i.p.) was administered to induce diabetes in male mice. Remote ischemic postconditioning stimulus was delivered using three short cycles of ischemia and reperfusion (5 min of left femoral artery occlusion followed by 5 min of reperfusion) after 30 min of coronary artery occlusion and during initiation of reperfusion. Remote postconditioning attenuated myocardial infarction, improved left ventricular end diastolic and systolic diameter, improved cardiac ejection fraction, and preserved left ventricular systolic pressure in response to ischemia–reperfusion in non-diabetic mice. However, remote ischemic postconditioning did not modulate ischemic reperfusion injury in diabetic mice [16].

Possible mechanisms

The different mechanisms that may contribute in attenuating the cardioprotective effects of remote conditioning in diabetics are discussed below (Fig. 1).

Remote ischemic preconditioning

Reperfusion injury salvage kinase (RISK) pathway

The RISK pathway refers to pro-survival kinases, which are activated during reperfusion phase of ischemia–reperfusion injury to confer cardioprotection. Indeed, this pathway includes a group of protein kinases including AKT, and ERK1/2, and their activation at the time of reperfusion decreases myocardial injury [18, 53]. Remote ischemia preconditioning produces cardioprotection against ischemia–reperfusion injury via activation of

Table 1 Summarized finding demonstrating the influence of diabetes on remote ischemic conditioning-induced cardioprotection

S. no.	Protocol	Effects	Mechanism of attenuated cardioprotective effects	References
Remote ischemic preconditioning				
1	• 4 cycles of 5 min of ischemia and 5 min of reperfusion • Left coronary artery ligation • Streptozotocin-induced diabetes (50 mg/kg) i.p.	• Diabetes did not attenuate all types of arrhythmia incidence • Diabetes failed to prevent RIPC following atrioventricular block	• Equally increased the RISK pathway (including AKT, ERK1/2, and GSK-3β) as compared to control	Hu et al. 2007
2	• Initial 4 cycles of 5 min remote ischemic preconditioning stimulus followed by additional 2 cycles of 10 min remote ischemic preconditioning stimulus (intensified remote ischemic preconditioning stimulus) • Langendroff model • Dialysate of diabetic patients (50–75 years)	• Dialysate of diabetic persons following RIPC failed to reduce infarct size	• Diabetes abolished the release of cardioprotective humoral factor during remote ischemic preconditioning	[23]
3	• Perfusion of human dialysate following remote ischemic preconditioning to isolated atrial trabeculae • Isolated atrial trabeculae subjected to ischemia–reperfusion injury • Diabetic and non-diabetic patients (50–75 years)	• Dialysate of diabetic person following RIPC did not further decrease infarct size	• Diabetes failed to increase remote ischemic preconditioning-induced increase in O-GlcNAc level	[24]
Remote ischemic perconditioning				
1	• 3 cycles of 5 min unilateral femoral vessel occlusion and 5 min reperfusion • Left coronary artery ligation • Acute hyperglycemia induced by 50% dextrose infusion	• Acute hyperglycemia following remote ischemic perconditioning attenuated the infarct size • Acute hyperglycemia following remote ischemic perconditioning increased the incidence and duration of arrhythmia	• Diabetes increase mTOR activity, oxidative stress, and decrease in LC3II/LC3I ratio (autophagy)	[4]
2	• Bilateral femoral artery occlusion for 15 min during myocardial ischemia • Left coronary artery ligation • Streptozotocin-induced diabetes (55 mg/kg) i.v.	• Remote ischemic perconditioning failed to reduce infarct size in diabetic rats	• Diabetes increased arginase and ROCK activity • Diabetes decreased NO level	Kiss et al. 2014
Remote ischemic postconditioning				
1	• 3 cycles of 5 min ischemia of left femoral artery occlusion followed by 5 min of reperfusion • Left femoral artery occlusion • Streptozotocin (150 mg/kg) i.p.	• Remote ischemic postconditioning failed to reduce infarct size in diabetic mice	• Diabetes increase in AMPKα and decrease autophagy	[16]

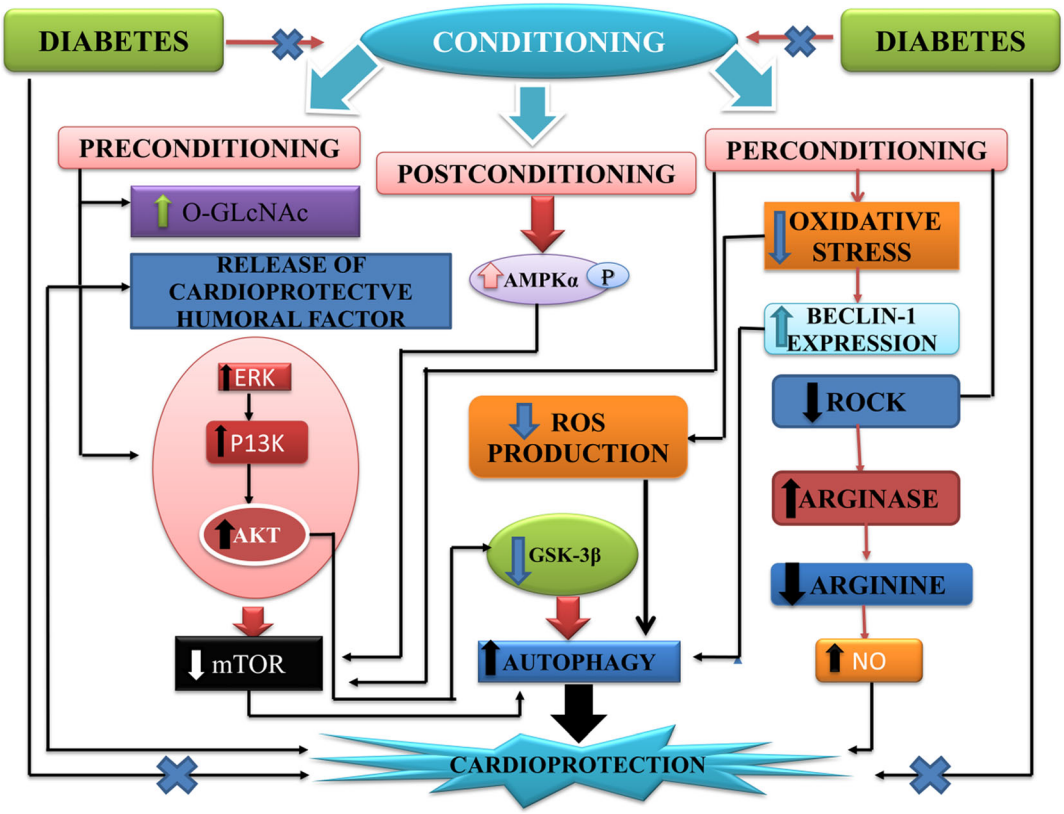

Fig. 1 Possible mechanisms that may be involved in abolishing conditioning-induced cardioprotection during diabetes

RISK pathway, and inhibition of GSK-3β (Ser 9) phosphorylation [18]. Hu et al. reported that remote preconditioning increases the levels of phosphorylated forms of ERK1/2, AKT, and GSK-3β during reperfusion phase. However, remote ischemic preconditioning increased the phosphorylation of these enzymes in the hearts of diabetic as well as in non-diabetic rats to a comparable degree. It suggests that diabetes does not impair the functioning or activation process of RISK pathway. Another study has shown that exogenous administration of H_2S donor confers cardioprotection in diabetic rats by activation of endogenous protective RISK pathway [31] suggesting that RISK pathway remains intact and is not impaired in diabetic conditions. Therefore, it may be proposed that impairment of pro-survival kinases of RISK pathway may not be contributing in attenuating remote preconditioning-induced cardioprotection in diabetic state [21].

Neural pathway

There have been studies including from our laboratory showing the involvement of neural pathways in mediating the cardioprotective effects of remote ischemic preconditioning [2, 57]. It has been reported that resection of femoral or the sciatic nerves partially blocks remote ischemic preconditioning-induced cardioprotection, while resection of both the nerves completely abolishes the cardioprotective effect of remote ischemic preconditioning [35]. The study of Jensen et al. proposed that there is a release of a cardioprotective humoral factor during remote ischemic preconditioning, which may be dialyzed and administered to rabbits to confer them cardioprotection against ischemia–reperfusion injury. It was also proposed that release of the cardioprotective factor is dependent on the presence of intact neural pathway. However, it is well reported that there is significant impairment in neural functioning during long-standing diabetes, which is manifested in the form of diabetic neuropathy [20]. Therefore, it is possible to propose that during long-standing diabetes, nerve injury in the form of diabetic neuropathy may inhibit the release of cardioprotective factor during remote ischemic preconditioning, which is manifested in the form of attenuation of the cardioprotection [23].

O-Linked β-*N*-acetylglucosamine (O-GlcNAc) glycosylation

O-GlcNAc is an intercellular carbohydrate, which results in a post-translational modification of proteins (cytoplasmic, nuclear, and mitochondrial) in response to changes in extracellular concentration of glucose. O-GlcNAc glycosylation is the post-translational modification of proteins in response to high glucose levels in which *N*-acetylglucosamine is linked to serine or threonine residues of intracellular proteins via O-

glycosidic linkage with the help of O-GlcNAc transferase (OGT). The levels of O-GlcNAc are increased during ischemic preconditioning to produce cardioprotection [24]. Remote ischemic preconditioning dialysate from non-diabetic volunteers augmented the levels of O-GlcNAc in isolated atrial trabeculae in comparison to control dialysate suggesting that an increase in O-GlcNAc may confer cardioprotection. However, remote ischemic preconditioning dialysate isolated from diabetic persons failed to augment the already raised O-GlcNAc levels due to diabetes [24]. Remote preconditioning-induced cardioprotection depends on O-GlcNAcylation and the levels of O-GlcNAc cannot increase beyond the limits in diabetic persons because these levels are already increased before remote preconditioning stimulus during diabetic conditions. Administration of azaserine (glutaminefructose-6-phosphate amidotransferase, GFAT, inhibitor) attenuated the increase in O-GlcNAc levels in the atrial tissue and also reduced the cardioprotective effects in response to remote ischemic preconditioning dialysate as well as diabetic control dialysate [24].

Remote ischemic perconditioning

Mechanistic target of rapamycin (mTOR) and AKT pathway

Baranyai et al. reported that remote perconditioning-induced cardioprotection was abolished during acute hyperglycemia due to activation of mTOR and AKT [4]. mTOR is serine/threonine kinase that crucially mediates energy metabolism and is present in two forms, mTOR complex 1 (mTORC1), which is inhibited by rapamycin, and mTOR complex 2 (mTORC2), which regulates cellular homeostasis, stress responses, energy metabolism, and autophagy [14, 62]. Baranyai et al. reported that mTOR (Ser2448) and S6 (Ser235/236) were phosphorylated during diabetes mellitus, indicating that the activity of mTOR complex 1 was increased in acute hyperglycemic animals. Furthermore, AKT phosphorylation at Ser473 was also increased in acute hyperglycemic animals. However, phosphorylation of AMPKα (Thr172) and ERK1/2 (Thr202/Tyr204) did not change in acute hyperglycemic animals in comparison to normal glycemic animals. It has been shown that remote perconditioning down-regulates mTOR [52]. There have been other studies showing an increase in mTOR and AKT activity during acute hyperglycemic condition [11]. It has also been reported that the elevation of mTOR and AKT signaling increases the extent of myocardial injury during ischemia [62]. Pre-treatment with rapamycin has been shown to attenuate the effect of increased levels of mTOR leading to improvement in the cardiac function resulting from cardiac ischemia–reperfusion injury in diabetic mice [67]. Therefore, it is possible to suggest that acute hyperglycemia may activate mTOR pathway and its upstream modulator AKT, which may abolish remote ischemic perconditioning-induced cardioprotection [4].

Oxidative stress

An increase in oxidative stress is a major pathogenic factor in ischemia–reperfusion injury [58]. Hyperglycemia promotes production of reactive oxygen species (ROS), which may be critically involved in the development of diabetic complications. The levels of functional glutathione peroxidase are reported to be significantly decreased in diabetic mice [34]. In type 2 diabetic patients, the levels of both enzymatic (glutathione peroxidase, superoxide dismutase, and catalase) and non-enzymatic (vitamin E and C, β-carotene, and retinol) antioxidants are relatively low in comparison to non-diabetic subjects [45]. Primarily, hyperglycemia leads to increased formation of oxygen free radicals in the cardiac tissue by causing interruption of electron transport chain, activation of NADPH oxidase, and uncoupling of nitric oxide synthase [1]. Accordingly, oxidative stress has been proposed as a link between hyperglycemia and increased tendency to ischemic heart injury [58]. Baranyai et al. reported that oxidative stress and nitrative stress were increased during acute hyperglycemia in rats, as indicated by the elevated levels of cardiac nitrative stress marker (3-nitrotyrosine) during hyperglycemia [4]. Thus, it is possible to suggest that an increase in oxidative stress and nitrative stress may possibly impair the cardioprotective effects of remote perconditioning.

Autophagy

It is a process of auto-digestion in which the lysosomes degrade cellular organelles and other molecules. It helps in maintaining cellular homeostasis and it also provides cytoprotective actions [16]. It is proposed that the process of autophagy is activated during ischemia and reperfusion to protect the heart [16]. A study conducted by Qian et al. has suggested that inhibition of autophagy decreases the recovery of heart contractility against ischemia–reperfusion injury as observed in the transgenic mice with impaired autophagy in comparison to the non-transgenic animals [44]. However, Baranyai et al. reported that the quantitative index of autophagy, measured in terms of ratio of LC3II/LC3I, was decreased during remote ischemic perconditioning in acute hyperglycemia. However, the other autophagy proteins including Beclin-1, total and Triton X-100-insoluble SQSTMI/p62, phosphor-ULK1 (Ser555), ATG7, and BNIP3 did not change in acute hyperglycemic animals [4]. There have been earlier studies documenting that the presence of high glucose concentration (levels between 17 and 30 mM) leads to reduction in autophagy in comparison to normal glucose concentration (5.5 mM) [29]. Therefore, it may be proposed that an

impairment in autophagy during diabetes may impair remote ischemic perconditioning-induced cardioprotection.

Rho A/Rho-associated kinase (ROCK) signaling pathway

ROCK is a serine/threonine protein kinase, which is an important component of intracellular signaling cascade [65]. RhoA is GTP binding protein and it activates ROCK, which exists in two isoforms (ROCK1 and ROCK2). During ischemia–reperfusion, there is upregulation of RhoA in the heart, which activates Rho kinase and the latter plays a significant role in myocardial injury [3, 66]. It is also reported that diabetes may upregulate the expression and actions of RhoA and ROCK [59]. It has been shown that remote perconditioning decreases the ROCK signaling and enhances the expression of endothelial nitric oxide synthase (eNOS) in normal rats. However, it failed to reduce ROCK activity and increase eNOS in diabetic rats. Furthermore, remote ischemic perconditioning failed to decrease arginase activity in diabetic rats in comparison to non-diabetic rats. Arginase degrades arginine and hence decreases the substrate for NO production. Remote perconditioning-induced cardioprotective effects were completely abolished in the presence of L-NMMA, an inhibitor of nitric oxide synthase, (10 mg/kg, i.v.) [27, 28]. Therefore, it may possible to suggest that a decrease in NO availability along with increase in ROCK activity during diabetes may abolish remote perconditioning-induced cardioprotection.

Remote ischemic postconditioning

Autophagy

Han and co-workers reported that remote ischemic postconditioning downregulates the levels of SQSTM1, increases the LC3-II/LC3-I ratio, and increases the number of autophagic vacuoles suggesting that activation of autophagy may be responsible for cardioprotection [16]. This contention was further supported by the finding that administration of 3-methyl adenine (3-MA), an autophagy inhibitor, attenuated remote postconditioning-induced cardioprotection in normal mice. However, remote postconditioning failed to activate autophagy in diabetic rats, and this effect was directly correlated to decrease in cardioprotection [16]. Therefore, it is possible to propose that diabetes may inhibit autophagy during remote postconditioning to abolish its cardioprotective effects.

Adenosine 5′-monophosphate-activated protein kinase (AMPK)

AMPK is an enzyme which senses ATP and it is activated during decrease in ATP levels such as in the case of hypoxia and decrease in glucose levels. In non-diabetic animals, remote ischemic postconditioning increased the phosphorylation of AMPK to increase the p-AMPKa (Thr172) levels suggesting that remote postconditioning-induced cardioprotection may be possibly due to an increase in AMPK activity [16]. However, the levels of phosphorylated AMPKα was not elevated in response to remote ischemic postconditioning in diabetic animals, suggesting that diabetes may inhibit AMPK activation and block cardioprotective effects of remote ischemic postconditioning [16]. Other studies have shown that ischemic postconditioning enhances AMPK phosphorylation to trigger cardioprotection [17]. Furthermore, the studies have also shown that diabetes decreases the AMPK activity and abolishes the cardioprotection [36].

Conclusion

Diabetes mellitus markedly abolishes the potential of remote pre/per/postconditioning stimuli to induce cardioprotection. The decrease in the release of humoral cardioprotective factors, O-GlcNAc signaling, and damage to the neural pathway due to diabetes may result in attenuating the cardioprotective effects of remote ischemic preconditioning. The protection conferred to the heart by remote ischemic perconditioning may be abolished in diabetic state owing to the activation of mTOR and AKT, increase in the oxidative stress, and upregulation of RhoA and ROCK. Diabetes may attenuate the cardioprotective activity of remote ischemic postconditioning as a consequence of decline in the activity of AMPK. The impairment of autophagy in diabetic state may be responsible for eliminating the cardioprotective effects of remote ischemic per and postconditioning.

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Compliance with ethical standards

Disclosure of potential conflicts of interest The authors declare no conflict of interests.

Research involving human participants and/or animals The study did not involve usage of animals or employment of human participants.

Informed consent The study did not involve participants of human volunteers.

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