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The Importance of Restoring the Adiponectin Signaling Pathway to Reduce Myocardial Reperfusion Injury in Diabetes

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COMMENTARY

The incidence of heart failure after an acute myocardial infarction (AMI) remains unacceptably high despite medical advances in the past several years (1). Therefore, the discovery of new drugs or strategies to reduce myocardial damage in patients with AMI is urgently warranted. This problem is exacerbated particularly in those affected by diabetes. Diabetes significantly reduces myocardial ischemic tolerance after a sudden coronary artery occlusion, thereby leading to increased ischemic and reperfusion (IR) injuries (2). During the past several years, ischemic postconditioning (IPo) has emerged as an efficient intervention to reduce reperfusion injury and infarct size in patients with AMI (3). It consists of very short repetitive episodes of IR applied at the immediate onset of reperfusion after a prolonged coronary artery occlusion. Unfortunately, previous experimental studies demonstrated that the beneficial effects of IPo are largely lost in the presence of diabetes, although the mechanisms underlying this phenomenon remain to be fully clarified (2).

In their study in this issue of *Diabetes*, Li et al. (4) demonstrate that type 1 diabetes abrogates the beneficial effects of IPo through the disruption of adiponectin signaling. Adiponectin is an adipocytokine that regulates glucose and fatty acid metabolism, exerting antioxidant, anti-inflammatory, and pro-survival effects (5). Adiponectin is also synthetized and secreted by cardiomyocytes, protecting against myocardial IR injury (5,6). Li et al. demonstrate that cardiac adiponectin levels are significantly reduced in response to IR, but this effect is dampened by IPo, which upregulates cardiac adiponectin levels in the early phase of reperfusion. IPo significantly reduced IR injury in wild-type mice, whereas it failed to be cardioprotective in systemic adiponectin knockout mice, thereby demonstrating that adiponectin is required for the beneficial effects of IPo. Additionally, it was found that IPo improved mitochondrial function, reduced oxidative stress, and increased nitric oxide levels in an adiponectin-dependent manner. Mechanistically, the beneficial effects of adiponectin in IPo appeared to be specifically mediated by the activation of adiponectin receptor 1 (AdipoR1) but not by AdipoR2, thereby confirming previous results demonstrating that AdipoR1 and AdipoR2 may regulate different mechanisms (7). Of note, IPo also increased the interaction between AdipoR1 and caveolin-3 (Cav3), a protein that appears to be critical for AdipoR1 function. This result is supported by evidence that the beneficial effects of adiponectin are lost in mice with Cav3 gene deletion (8). IPo significantly increased myocardial levels of signal transducer and activator of transcription 3 (STAT3) phosphorylated at Ser^{727}, which is known to localize to mitochondria (9). These effects also appear to be mediated by adiponectin and were required for the cardioprotective effects of IPo. Interestingly, the adiponectin/AdipoR1/mitochondrial STAT3 (mitoSTAT3) pathway was found to be disrupted in the hearts of rats with streptozotocin-induced diabetes. IPo failed to be protective and to increase myocardial adiponectin levels during reperfusion in diabetic animals. In addition, Li et al. found that diabetes inhibited IPo-induced AdipoR1-Cav3 interaction. This data suggest that diabetes disrupts adiponectin signaling by affecting both adiponectin levels and AdipoR1 signaling.

Several mechanistic aspects of this study remain to be clarified. The signaling pathways through which cardiac adiponectin levels are regulated by IPo and diabetes remain unknown. Previous studies demonstrated that SIRT1 induces adiponectin upregulation through FOXO1-dependent mechanisms (10). Interestingly, SIRT1 signaling protects

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against IR injury and is impaired in diabetes (2,11). Additionally, PPAR-γ activation induces the upregulation of adiponectin in cardiomyocytes (12) and protects against IR (6). It would be prudent to investigate whether these signaling pathways are involved in the IPo-induced adiponectin signaling activation.

The mechanisms through which the AdipoR1-Cav3 interaction is disrupted by diabetes also remain unclear. It is possible that the increased oxidative stress in the diabetic myocardium may play a role as caveolin proteins are negatively regulated by reactive oxygen species (ROS) (13). It also remains unclear how adiponectin activates STAT3 in response to IPo. Of note, both extracellular signal–related kinases and c-Jun N-terminal kinases are able to phosphorylate STAT3 at Ser^{727}, and adiponectin was shown to be able to activate these kinases (14–16).

The mechanisms through which STAT3 activation reduces reperfusion injury and increases the activities of mitochondrial complex I, IV, and V also warrant further clarification. Previous work showed that mitoSTAT3 enhances complex I and II activities by directly interacting with these complexes and through a mechanism that is independent of its transcription factor functions (9). In addition, STAT3 was shown to protect against IR by upregulating the ROS scavengers metallothioneins (17), suggesting that STAT3 may improve mitochondrial function by directly regulating complex activity and by reducing ROS.

Adiponectin may be responsible for the protective effects of IPo through the modulation of other adaptive molecular pathways distinct from STAT3 (Fig. 1). Adiponectin activates AMPK, which protects the heart against IR by regulating myocardial metabolism and mitochondrial function (5). Adiponectin upregulates autophagy, which may reduce reperfusion injury by eliminating damaged mitochondria through mitophagy (18). Adiponectin inhibits NADPH oxidase activity, which contributes to ROS generation and IR injury (5). Adiponectin may reduce IR injury through the activation of sphingosine-1-phosphate signaling (19). Adiponectin activates endothelial nitric oxide synthase/nitric oxide signaling, which is a major mediator of IPo-induced oxidative stress inhibition and cardioprotection (5). Of note, all of these potential beneficial effects of adiponectin signaling are impaired in diabetes. Interestingly, it was recently demonstrated that the shift of cardiac macrophages away from the M1 phenotype is associated with cardioprotection against IR injury (20). Diabetes is associated with a more prominent macrophage inflammatory phenotype, whereas adiponectin was shown to polarize macrophages away from the M1 phenotype and toward the M2 phenotype (21). This could be another mechanism through which adiponectin may mediate cardioprotective effects of IPo.

Therefore, if confirmed in animal models of type 2 diabetes, the results of the study by Li et al. (4) strongly suggest that a combination strategy based on both IPo and the restoration of adiponectin/AdipoR1/mitoSTAT3 signaling may represent a potential efficient intervention to reduce reperfusion injury after an AMI in patients with diabetes. Future studies are needed to understand how to restore adiponectin signaling in the diabetic heart. The administration of exogenous adiponectin or AdipoRon, an activator of AdipoRs, may be appropriate for the

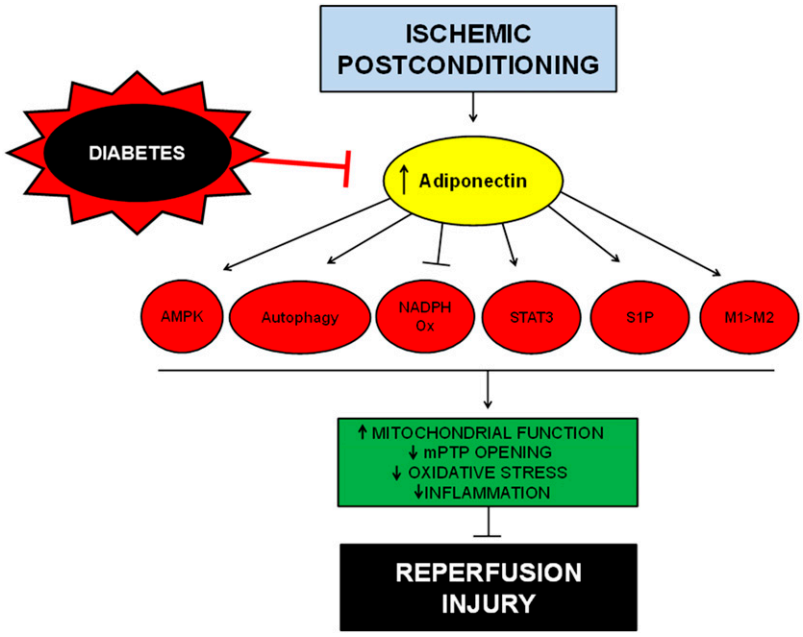

Figure 1—IPo-induced adiponectin protects against IR. Schema representing the molecular mechanisms through which IPo-dependent adiponectin activation may protect against IR. M1>M2, switch from M1 toward M2 macrophage phenotype; mPTP, mitochondrial permeability transition pore; NADPH Ox, NADPH oxidase; S1P, sphingosine-1-phosphate.

associated insulin-sensitizing effects. However, specific interventions to preserve the AdipoR1-Cav3 interaction may be required. Alternatively, STAT3 activators may be useful to directly activate the downstream target mediating the beneficial effects of adiponectin activation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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