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Review article

Ischemia reperfusion injury, ischemic conditioning and diabetes mellitus

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ABSTRACT

Ischemia/reperfusion, which is characterized by deficient oxygen supply and subsequent restoration of blood flow, can cause irreversible damages to tissue. Mechanisms contributing to the pathogenesis of ischemia reperfusion injury are complex, multifactorial and highly integrated. Extensive research has focused on increasing organ tolerance to ischemia reperfusion injury, especially through the use of ischemic conditioning strategies. Of morbidities that potentially compromise the protective mechanisms of the heart, diabetes mellitus appears primarily important to study. Diabetes mellitus increases myocardial susceptibility to ischemia reperfusion injury and also modifies myocardial responses to ischemic conditioning strategies by disruption of intracellular signaling responsible for enhancement of resistance to cell death.
The purpose of this review is twofold: first, to summarize mechanisms underlying ischemia reperfusion injury and the signal transduction pathways underlying ischemic conditioning cardioprotection; and second, to focus on diabetes mellitus and mechanisms that may be responsible for the lack of effect of ischemic conditioning strategies in diabetes.

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1. Introduction

The heart is one of the most energy demanding tissues in the body and is totally dependent upon oxidative phosphorylation to supply the large amount of ATP required for continuous contraction and relaxation. Ischemia, caused by disruption in blood flow leads to deficient oxygen supply to tissue. This results in cessation of oxidative phosphorylation, causing decrease in tissue ATP and creatine phosphate, and concomitant rise in ADP, AMP and Pi concentrations. Glycolysis is activated, but is unable to produce the required level of ATP. The heart rapidly ceases to beat as the contractile machinery is inhibited by elevated Pi and ADP, combined with the decreasing pH from the accumulation of glycolytic lactic acid [1]. Short duration ischemia is associated with full recovery of the tissue after reperfusion, while prolonged ischemia can lead to cell death. The extent of tissue injury is influenced by both the magnitude and duration of ischemia. Immediate restoration of blood flow remains the mainstream treatment. Reperfusion delivers oxygen and nutrients to support aerobic metabolism and ATP generation, and normalizes extracellular pH by washing out accumulated H^+ ions. However, reperfusion may paradoxically exacerbate tissue injury, and this additional damage is called reperfusion injury.

Mechanisms contributing to the pathogenesis of ischemia reperfusion injury are multifactorial and complex but also highly integrated. Increases in cellular calcium and reactive oxygen species (ROS), initiated during ischemia and then amplified upon reperfusion are thought to be the main mediators of reperfusion injury. Mitochondrial dysfunction also plays an important role, both in the production of ROS and as a target for downstream effects of both ROS and calcium overload [1–5].

Extensive research has focused on increasing heart tolerance to ischemia reperfusion injury using conditioning strategies. Brief episodes of coronary ischemia reperfusion preceding (ischemic preconditioning) or following (ischemic postconditioning) sustained myocardial ischemia reperfusion reduce infarct size. Even ischemia reperfusion in organs remote from the heart provides cardioprotection (remote ischemic conditioning) [6–10]. Diabetes is a common comorbidity in patients with cardiovascular disease [11]. Despite progress in coronary intervention strategies, diabetes mellitus is still associated with higher mortality after acute myocardial infarction. Diabetes mellitus increases myocardial susceptibility to ischemia reperfusion injury and also modifies myocardial responses to ischemic conditioning strategies by disruption of intracellular signaling responsible for conditioning-induced enhancement of resistance to cell death [12–16]. These alterations in the diabetic heart appear to underlie the poor prognosis of diabetic patients after acute myocardial infarction.

The purpose of this review is twofold. First, to summarize mechanisms underlying ischemia reperfusion injury and signal transduction pathways underlying ischemic conditioning-related cardioprotection. Second, to focus on diabetes mellitus and mechanisms that may be responsible for the lack of effect of ischemic conditioning strategies in the diabetic heart.

2. Part I: ischemia–reperfusion injury and ischemic conditioning

2.1. A. Mechanisms of ischemia reperfusion injury

The mechanisms contributing to the pathogenesis of ischemia reperfusion injury are multifactorial, complex, and moreover highly integrated. Processes as varied as calcium overload, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, apoptosis, protein kinases activation, and inflammation all play an important role and are also inter-related [2–5].

2.1.1. Calcium overload

When oxygen delivery to tissue is impaired, cells undergo a transformation from aerobic to anaerobic metabolism, switching to glycolysis for ATP generation. This leads to an accumulation of lactates, protons, and NAD^+, and decreases cell pH. Cells restore pH by extruding H^+ ions for Na^+ through the Na^+/H^+ exchanger. Na^+ ions are then exchanged for Ca^{2+} by the Na^+/Ca^{2+} exchanger[3]. The increase in cytosolic Ca^{2+} is exacerbated upon reperfusion, because the washout of accumulated extracellular H^+ ions further increases the proton gradient across the cell membrane, thereby accelerating Na^+/H^+ exchanger function[3]. In addition to changes in transmembrane Ca^{2+} transport during ischemia–reperfusion, Ca^{2+} transport across the sarcoplasmic reticulum is also affected. Ca^{2+} reuptake into the sarcoplasmic reticulum by the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) is impaired, while Ca^{2+} release through the ryanodine receptor is enhanced (Fig. 1) [4–17]. (See Fig. 2.)

Calcium overload activates a variety of systems, all of which can contribute to cell injury following ischemia reperfusion. Excess Ca^{2+} is taken into the mitochondria via the mitochondrial Ca^{2+} uniporter, a protein that uses the negative mitochondrial transmembrane potential to drive uptake of the positively charged Ca^{2+} ions into the matrix. However, when Ca^{2+} levels in the mitochondria become excessive, Ca^{2+} binds and activates the Ca^{2+} binding domains of the mitochondrial permeability transition pore (mPTP), leading directly to mPTP opening and causing cell death (Fig. 1) [18]. The calpains are another target for calcium overload. This family of cysteine proteases is activated by increased Ca^{2+} and degrades intracellular proteins such as cytoskeletal, endoplasmic reticulum and mitochondrial proteins. On the other hand, the endogenous inhibitor of calpains, calpastatin, is often degraded during ischemia reperfusion, which further enhances calpain availability and ischemia reperfusion injury [1]. Finally, calcium overload can lead to the generation of calcium pyrophosphate complexes and the formation of uric acid, both having the possibility to bind to