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Novel therapeutic strategies for cardioprotection

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ABSTRACT

The morbidity and mortality from ischemic heart disease (IHD) remain significant worldwide. The treatment for acute myocardial infarction has improved over the past decades, including early reperfusion of occluded coronary arteries. Although it is essential to re-open the artery as soon as possible, paradoxically this leads to additional myocardial injury, called acute ischemia–reperfusion injury (IRI), for which currently no effective therapy is available. Therefore, novel therapeutic strategies are required to protect the heart from acute IRI in order to reduce myocardial infarction size, preserve cardiac function and improve clinical outcomes in patients with IHD.

In this review article, we will first outline the pathophysiology of acute IRI and review promising therapeutic strategies for cardioprotection. These include novel aspects of mitochondrial function, epigenetics, circadian clocks, the immune system, microvesicles, growth factors, stem cell therapy and gene therapy. We discuss the therapeutic potential of these novel cardioprotective strategies in terms of pharmacological targeting and clinical application.

Contents

Abbreviations: AAV, adeno-associated viral; ACS, acute coronary syndrome; ADORA2B, A2B adenosine receptor; AMI, acute myocardial infarction; ATP, adenosine triphosphate; BM, bone marrow; CABG, coronary artery bypass graft; CCM, cardiomyocyte clock mutant; CHD, coronary heart disease; COX, cyclooxygenase; DAMP, danger-associated molecular pattern; DPPIV, dipeptidyl peptidase IV; EGFR, epidermal growth factor receptor; ESCRT, endosomal sorting complexes required for transport; FGF, fibroblast growth factor; HDAC, histone deacetylase; HGF, hepatocyte growth factor; HIF, hypoxia inducible factor; HSP, heat shock protein; IFM, interfibrillar mitochondria; IGF, insulin-like growth factor; IHD, ischemic heart disease; IL, interleukin; IRI, ischemia–reperfusion injury; LVEF, left ventricular ejection fraction; MI, myocardial infarction; miRNA, microRNA; MPT, mitochondrial permeability transition; MPTP, mitochondrial permeability transition pore; NADPH, nicotinamide adenine dinucleotide phosphate-oxidase; NcRNA, noncoding RNA; NF, nuclear factor; NOS, nitric oxide synthase; PCI, percutaneous coronary intervention; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator-activated receptor; PPCI, primary percutaneous coronary intervention; PTEN, phosphatase and tensin homologue; RISC, RNA-induced silencing complexes; RIP, receptor-interacting protein; ROS, reactive oxygen species; SR, sarcoplasmic reticulum; SSM, sub-sarcolemmal mitochondria; STEMI, ST-elevation myocardial infarction; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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1. Introduction

Ischemic heart disease (IHD) is the leading cause of death and disability globally. The pathological consequences of IHD arise from the detrimental effects of acute ischemia–reperfusion injury (IRI) resulting in cardiomyocyte death, cardiac failure, arrhythmias and patient death. The major clinical settings in which the heart is subjected to acute IRI include:

(1) the acute ST-segment elevation myocardial infarction (STEMI) patient presenting with acute myocardial ischemia arising from a thrombotic occlusion in the coronary artery at the site of a ruptured atherosclerotic plaque, who is reperfused by primary percutaneous coronary intervention (PPCI) to restore coronary blood flow in the infarct-related artery. Final MI size and resultant left ventricular ejection fraction (LVEF) are major determinants of clinical outcomes in this patients group. Although strategies are already in place to shorten the chest pain to PPCI time and improve the process of myocardial reperfusion via PPCI, there is currently no effective therapy for preventing 'myocardial reperfusion injury' — this is a form of myocardial injury and cardiomyocyte death which paradoxically occurs upon reperfusion of the ischemic myocardium and is due to mitochondrial calcium overload, oxidative stress, mitochondrial dysfunction, and cardiomyocyte hyper-contracture (reviewed in Yellon, 2007);
(2) the IHD patient undergoing coronary artery bypass graft (CABG) surgery, in whom the heart is subjected to global ischemic injury as the heart is put onto cardiopulmonary bypass followed by global reperfusion injury as the heart is taken off cardiopulmonary bypass. Despite current cardioprotective strategies such as hypothermia and cardioplegia, a significant amount of perioperative myocardial injury and cardiac dysfunction occurs in response to acute IRI (Venugopal et al., 2009);
(3) cardiac transplantation, in which the heart is also subjected to global acute IRI despite current cardioprotective strategies (hypothermia, cardioplegia) (Fischer & Glas, 2013).

In all of these clinical settings, patient morbidity and mortality remains significant, and so novel therapeutic interventions which are capable of limiting cardiomyocyte death are required to improve clinical outcomes in patients with IHD. A variety of therapeutic interventions have been investigated over the years to combat acute IRI, although the results of these studies in the clinical setting have been largely disappointing, the reasons for which are discussed elsewhere (Hausenloy et al., 2010, 2013). Therefore, new treatment strategies directed to novel targets for cardioprotection are needed to limit myocardial infarct size and preserve cardiac function, thereby preventing the onset of heart failure and improve patient survival. In this article we review some of the more promising therapeutic strategies for cardioprotection, from their mechanisms underlying their protective effect to their potential clinical application.

2. Novel cardioprotective strategies

2.1. Novel aspects of mitochondrial function

During normoxia, mitochondria consume large amounts of oxygen to produce ATP at complex V of the respiratory chain. When the heart becomes ischemic, the electron flow through the respiratory complexes is inhibited and mitochondrial oxygen consumption as well as ATP production decrease (Lesnefsky et al., 1997). Instead, myocardial ATP produced in the cytosol by anaerobic glycolysis is now consumed by mitochondria to maintain their inner membrane potential. Upon reperfusion oxidative phosphorylation is restored in the remaining viable cells, ATP production increases and may contribute to the re-establishment of cellular ion homeostasis, but paradoxically increased ATP production may also contribute to reperfusion injury. During ischemia, the cardiomyocyte cytosol becomes overloaded with calcium (Ca^{2+}). During reperfusion, when ATP production is restored, Ca^{2+} is taken up into the sarcoplasmic reticulum (SR) by the SR Ca^{2+} ATPase. Once the storage capacity of the SR is exceeded, Ca^{2+} is released again from the SR in a cycling process, giving rise to a pattern of "Ca^{2+} oscillations" that may eventually lead to hypercontracture of cardiomyocytes, membrane disruption and subsequent cell death via apoptosis and necrosis (Piper et al., 2006).

Mitochondria also take up cytosolic Ca^{2+} via the Ca^{2+} uniporter. In the presence of elevated cytosolic Ca^{2+} concentration, mitochondria can become Ca^{2+} overloaded especially since mitochondria are exposed to particularly high local Ca^{2+} concentration due to their close proximity with the SR (<100 nm distance). This tight communication between both organelles may have pathophysiological consequences during ischemia/reperfusion injury (Ruiz-Meana et al., 2010). The consequences of Ca^{2+} overload are outlined below.

Apart from ATP, mitochondria generate reactive oxygen species (ROS) (Balaban et al., 2005) from different sources, one of them being the respiratory chain itself — mainly at complexes I and III. Here, electrons from the electron transport chain can be transferred to oxygen, which results in the formation of superoxide anions. ROS are also produced by monoamine oxidases located at the outer mitochondrial membrane, which transfer electrons from amine compounds to oxygen leading to hydrogen peroxide formation (Fridovich, 1995). Furthermore, the cytosolic protein $p66^{Shc}$ becomes phosphorylated under stress conditions and shuttles into the mitochondrial intermembrane space, where it oxidizes reduced cytochrome c and thereby results in peroxide formation (Giorgio et al., 2005). ROS formation is increased during ischemia (Vanden Hoek et al., 1997) and a further burst of ROS occurs early after reperfusion (Kevin et al., 2003). Increased ROS formation is causally involved in cell death after ischemia/reperfusion (Vanden Hoek et al., 1997; Kupatt et al., 2004) and ROS scavenging at reperfusion reduces reversible and irreversible cellular injury. Accordingly, hearts from $p66^{Shc}$ knockout mice are protected from ischemia/reperfusion injury in vitro (Carpi et al., 2009), and inhibition of monoamine oxidase reduces infarct size following ischemia/reperfusion injury in vivo (Bianchi et al., 2005).

The burst of ROS at the onset of reperfusion facilitates the formation of the mitochondrial permeability transition (MPT), a sudden increase in the inner membrane permeability to solutes with molecular weights up to 1.5 kDa, leading to mitochondrial depolarization and ATP depletion (Di Lisa et al., 2007). Subsequently, mitochondrial matrix volume increases and induces rupture of the outer mitochondrial membrane. This leads to loss of pyridine nucleotides and thereby to inhibition of electron flow along protein complexes of the electron transport chain. MPT is facilitated by Ca^{2+} ions, inorganic phosphate and mitochondrial depolarization, i.e. conditions occurring during ischemia/reperfusion (Heusch, 2013). Conversely, MPT is inhibited at increased mitochondrial membrane potentials, high concentrations of protons, magnesium ions, adenine nucleotides, and nitric oxide. Also, knockout of cyclophilin D delays Ca^{2+}-induced MPT in isolated liver and cardiac mitochondria, and protects fibroblasts from H_2O_2-induced loss of mitochondrial membrane potential (Baines et al., 2005). However, cyclophilin D-deficiency