Commentary

PPAR-γ and AMPK – Advantageous targets for myocardial ischemia/reperfusion therapy

Alex Morrison, Ji Li *

Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, University at Buffalo-SUNY, 3435 Main Street, Buffalo, NY 14214, United States

ABSTRACT

Ischemic heart disease stands as the number one leading cause of death in the United States. Current interventions rely on the immediate restoration of blood flow to the ischemic area; however, this in turn may trigger a series of undesirable events that are further injurious to the myocardium, termed ischemia/reperfusion (I/R) injury. Therefore, there is a need for novel therapeutic strategies aimed at limiting the extent of myocardial injury. Yet, the molecular mechanisms responsible for I/R injury remain largely indefinable. Research efforts are currently investigating various signaling mechanisms to be used for potential targets limiting cardiac injury due to such cardiovascular events. In this review, we highlight two potential molecular targets, PPAR-γ and AMPK, which have been extensively reported to have various cardioprotective capabilities against I/R injury. Although functionally different, the pathways these proteins mediate seem to intersect and possibly act synergistically potentiating a cardioprotective response.

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1. Introduction

Ischemic heart disease and myocardial infarction contribute to the leading cause of death in the United States, effecting approximately one million patients each year [1]. Emergent restoration of coronary patency via anticoagulants, thrombolytics, and percutaneous coronary intervention is currently the gold standard for patients presenting with acute ischemic events. However, prolonged ischemia followed by immediate reperfusion has been shown to often escalate the process of cell death and increase the extent of infarction [2]. This process known as ischemia/reperfusion (I/R) injury although undesirable appears to be inevitable. Thus, there is an increasing need for novel therapeutic strategies limiting the extent of myocardial infarction due to I/R injury.

As current clinical treatments and interventions are aimed at immediate recanalization despite the known consequences of reperfusion injury, addressing potential therapeutic targets pertaining to cardiac metabolism, inflammation, oxidative stress, and apoptosis have yet to be implemented [3]. As such, this review is intended to bring out the importance of two metabolic molecular targets, Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ), and AMP-Activated Protein Kinase (AMPK), which have been demonstrated in the literature extensively to possess cardiopro-

tective properties in the incidence of I/R. Although these targets are functionally different, the interplay and modulation of the pathways these targets mediate seem to be inter-related. Despite these findings, modulating these pathways pharmacologically is limited exclusively for patients with type 2 diabetes. In this review, we will discuss the pathophysiological mechanisms and metabolic challenges contributing to I/R injury. In addition, we will outline the mechanisms in detail that are associated with each pathway, and how these can contribute to potential therapeutic strategies aimed at mitigating myocardial infarction.

2. Mechanisms of ischemia/reperfusion injury

Myocardial ischemia occurs due to the lack or interruption of blood flow to the myocardium. Immediately after the onset of ischemia, there is a significant change in the energy balance, or extreme depletion of ATP. As a result, the heart adapts, due to an abrupt inhibition of fatty acid oxidation and increases the flux toward anaerobic respiration through glycolysis. Consequently, glucose transport into the myocardium is increased via translocating GLUT1 and GLUT4 to the sarcolemma [4]. Ischemia also induces the accumulation of intracellular calcium, sodium, and hydrogen ions that can develop into acidosis within the myocardium [5]. The substantial drop in the production of ATP during ischemia will also in turn inhibit the membranous sodium/potassium-ATPase. The accumulation of these ions and disruption of this equilibrium in the cardiomyocyte can lead to protease activation, osmotic

swelling, sarcolemmal rupture, and eventually cell death [6]. Recent evidence has also suggested that the induction of autophagy during ischemia is a protective process by which the cardiomyocyte is able to salvage ATP by the clearance of protein aggregates and damaged organelles [7]. Although protective during ischemia, the induction of autophagy during reperfusion is suggested to be detrimental through distinct mechanisms [8].

Upon reperfusion of the myocardium, there is a rapid increase in intracellular calcium that will induce the opening of the mitochondrial permeability transition pore (mPTP). Consequently, this results in the dissipation and uncoupling of the electrochemical gradient of the inner mitochondrial membrane and the release of an enormous amount of highly reactive and highly destructive reactive oxygen species (ROS) [9]. This increase in ROS and oxidative stress contributes tremendously to the increase in accelerated cell death at the onset of reperfusion [6]. Moreover, ROS has been suggested to contribute to the "no-reflow phenomenon" seen post-reperfusion [10]. Thus, despite restoration of blood flow to the ischemic area, the microvasculature becomes clogged with vascular debris preventing adequate perfusion [9]. Reperfusion also disrupts and increases the permeability of the endothelium. As a result, the bioavailability of nitric oxide (NO) is depleted and there is increased intrusion of inflammatory cells, vasculodestructive cytokines, cell adhesion molecules, and a further increase in ROS [5,9].

3. Cardioprotection via PPAR-γ modulation

The Peroxisome Proliferator-Activated Receptors (PPARs) reside within a superfamily of ligand-activated nuclear receptors that bind to specific DNA regulatory elements forming heterodimers from the enabled interaction with the retinoid X receptor (RXR) [11]. The PPAR family composes of three members, PPAR-α, β/δ, and γ, of which are all known to have slightly different regulatory effects on their ability to modulate lipid metabolic genes [12]. PPAR-α and PPAR-β/δ are known to be significantly expressed in cardiomyocytes and are thought to play a major role in regulating fatty acid uptake and the expression of fatty acid oxidation genes [13,14]. Interestingly, both PPAR-α and PPAR-β/δ have been demonstrated to be cardioprotective during I/R injury by modulating PI3K/Akt and NO [15], decreasing inflammatory cytokines, and up-regulating pro-survival signaling such as Bcl-2 and Akt [16].

The role of PPAR-γ in the heart still appears to remain largely elusive. PPAR-γ has undoubtedly received the most attention in the literature regarding its pronounced insulin sensitizing abilities and beneficial, although controversial effects on the heart [17]. Moreover, PPAR-γ activation is associated with pleiotropic effects in the vasculature such as exhibiting anti-inflammatory, anti-oxidative, anti-apoptotic, and anti-hypertensive functions [18]. Interestingly, compared to the rest of the PPARs, PPAR-γ is expressed at the lowest abundance in cardiomyocytes [19] and has been reported to only reach approximately 30% of the expression level compared to its expression in adipocytes [20].

The natural ligands of PPAR-γ include fatty acid metabolites such as 9- and 13-hydroxyocta-decadienoic acid, 12- and 15-hydroxyeicosatetaenoic acid, and prostaglandins, with the major ligand being 15 deoxy-12,14-prostaglandin J2 (15-dPGJ2) [21]. Synthetic ligands of PPAR-γ include a group of anti-diabetic drugs known as the thiazolidinediones (TZDs). The TZDs that are currently approved for insulin sensitization in type 2 diabetic patients include rosiglitazone (RGZ) and pioglitazone (PGZ) [22]. Other TZDs also exist such as ciglitazone, and troglitazone, which are only directed for use experimentally. All of these ligands, both endogenous and synthetic, have become of a particular interest due to their ability to decrease myocardial infarction [23].

Of all the PPAR-γ ligands, RGZ is recognized as the most selective and most potent [24] making it an ideal candidate for studying the effects of PPAR-γ in the heart. However, the use of this drug remains controversial [25] as recent large scale meta-analyses and clinical trials have indicated that long-term use of RGZ in type 2 diabetic patients is associated with an increased risk in heart failure and myocardial infarction [17]. Results of the Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) suggest that PGZ may be a safer alternative to RGZ for long-term glucose control in diabetic patients [22]. PGZ has also been shown to be cardioprotective against I/R injury in vivo [26]. Yet the use of RGZ in the experimental [27] and clinical setting [28] of I/R has suggested that the use of RGZ modulating the action of PPAR-γ has warranted further investigation due to its ability to stimulate cardioprotective mechanisms and its selectivity to PPAR-γ.

As inflammation has been widely accepted to play an important role in exacerbating I/R injury, the activation of PPAR-γ via TZDs such as RGZ and troglitazone has been shown to inhibit the activation of NF-κB and the release pro-inflammatory cytokines such as TNF-α in cardiomyocytes [29]. Similarly, the administration of an endogenous PPAR-γ ligand is able to limit I/R injury by reducing neutrophil infiltration, TNF-α production, and NF-κB activation in a PPAR-γ-dependent fashion [30]. In addition, PPAR-γ activation with RGZ in vivo has been shown to decrease I/R injury largely due to its anti-inflammatory properties by decreasing neutrophil and macrophage infiltration into the myocardium as well as down-regulating intracellular adhesion molecule-1 (ICAM-1) and monocyte chemoattractive protein-1 (MCP-1) [27]. RGZ has also been shown to protect the heart against I/R injury due to inhibiting vascular cell adhesion molecule-1 (VCAM-1), P-selectin, and E-selectin thereby mitigating leukocyte recruitment to the ischemic area [31] (Fig. 1).

c-Jun N-terminal Kinase (JNK) has emerged as an important stress kinase in the heart, and when activated, can lead to detrimental effects via pro-inflammatory signaling, and when down-regulated appears to be cardioprotective [32]. Our group (unpublished data) and others such as Khandoudi et al. suggest that RGZ is cardioprotective due to its ability to down-regulate p-JNK signaling through a PPAR-γ-dependent mechanism [33]. Additionally, RGZ has been shown to exert potent anti-inflammatory properties in patients by down-regulating cardiovascular destructive markers such as NF-κB activation, TNF-α, MCP-1, and C-Reactive Protein (CRP) [34].

TZD therapy for I/R injury has also been shown to mediate other cardioprotective signaling mechanisms such as Akt, a pro-survival/anti-apoptotic protein (Fig. 1). For instance, RGZ treatment to cardiomyocytes during hypoxia/reoxygenation up-regulates p-Akt signaling that in turn prevents cardiomyocyte apoptosis via a PPAR-γ-dependent mechanism [35]. Moreover, RGZ administration to diabetic rats mitigated I/R injury due to increasing the phosphorylation levels of Akt [36]. Consistent with these results, our group (unpublished data) and others have shown that myocardial protection with RGZ decreases infarction in mice through an Akt-dependent mechanism [30]. Furthermore, endogenous PPAR-γ ligand administration to mice resulted in significant cardioprotection by the increase in p-Akt during reperfusion [30]. A similar PPAR-γ-dependent cardioprotective mechanism is also shown by the administration of PGZ to rabbits whereby p-Akt is up-regulated [26]. Liu et al. have also demonstrated that by agonizing the PPAR-γ signaling pathway, ERK1/2 activity is up-regulated (anti-apoptotic), p38 MAPK activity is down-regulated (pro-apoptotic), and caspase-3 activity is significantly decreased when rabbits are subjected to I/R [37].

Other PPAR-γ-dependent cardioprotective effects can be attributable to antioxidative mechanisms (Fig. 1). Recent studies