Review

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Cardioprotective mechanism of FTY720 in ischemia reperfusion injury

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Cardioprotection is a very challenging area in the field of cardiovascular sciences. Myocardial damage accounts for nearly 50% of injury due to reperfusion, yet there is no effective strategy to prevent this to reduce the burden of heart failure. During last couple of decades, by combining genetic and biomolecular studies, many new drugs have been developed to treat hypertension, heart failure, and cancer. The use of percutaneous coronary intervention has reduced the mortality and morbidity of acute coronary syndrome dramatically. However, there is no standard therapy available that can mitigate cardiac reperfusion injury, which contributes to up to half of myocardial infarcts. Literature shows that the activation of sphingosine receptors, which are G protein-coupled receptors, induces cardioprotection both *in vitro* and *in vivo*. The exact mechanism of this protection is not clear yet. In this review, we discuss the mechanism of ischemia reperfusion injury and the role of the FDA-approved sphingosine 1 phosphate drug fingolimod in cardioprotection.

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Introduction

Cardioprotection

Cardiovascular diseases are the most common cause of mortality worldwide and an estimated 17.5 million deaths annually, i.e. one-third of global deaths (World Health Organization, 2016). During the last century, major advances had been made in cardiovascular sciences from noninvasive to interventional procedures such as coronary artery bypass graft surgery (CABG) and cardiac transplantation. Despite all the advances, cardiovascular diseases continue to be the most common cause of morbidity and mortality all over the world. This poses a huge financial burden on the health care system. Myocardial reperfusion is the treatment of choice for acute coronary syndrome (ACS), but abrupt restoration of blood supply exacerbates the tissue injury caused by ischemia, a process called ischemia/reperfusion injury (IRI). One of the proposed mechanisms of this phenomenon is reperfusion-induced imbalance between vasodilatory and vasoconstrictive substances [1]. Efforts to find ways to prevent and counter this injury have triggered the exploration of a whole new concept of cardioprotection.

Currently, 'myocardial IRI' is a hot topic of research and discussion to prevent irreversible myocardial damage and protect ventricular dysfunction, which in turn leads to heart failure. Cardioprotection is usually defined as 'all mechanisms and means that contribute to the preservation of the heart by reducing or even preventing myocardial damage' [2]. Unfortunately, the results of most of the animal studies could not be reproduced in human settings probably due to fundamental differences in the associated risk factors and comorbidities [3], [4].

Myocardial protection related to ischemia-reperfusion injury

In recent decades, numerous studies have shown that the myocardial cells possess several coping mechanisms aiming to limit the damage of ischemia/reperfusion. These processes are not limited to the myocardium but

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are also activated at areas both near and far from the heart, and they impart protection both in the acute phase after ACS and minimize the long-standing effects of myocardial infarction (MI).

The cellular mechanisms underlying certain phenomena of myocardial cell protection from ischemia/reperfusion (such as pre-conditioning and post-conditioning) remain to be clarified, but they are likely to be numerous and may include elements outside the myocardium. Lately, it has been discovered that ischemic pre- and post-conditioning affects not only cardiomyocytes but also the coronary vasculature by increasing the synthesis of nitric oxide (NO) and by other mechanisms [5]. Furthermore, circulating blood cells play a vital role in cardioprotection [6], [7]. Platelets and red cells confer cardioprotection by releasing several vesicles, e.g. exosome and micro vesicles (MVs), into the blood. Their cardioprotective role is proven by the fact that they are increased during ischemia and reperfusion and their administration reduces post-reperfusion myocardial damage and stimulated revascularization [7]. Platelets play a double role in IRI. They produce various cardioprotective agents, e.g. MVs and platelet activating factor; in contrast, cytokines produced by them are detrimental to cardiomyocytes [8]. The use of drugs to mimic the phenomenon of pre- or post-conditioning *in vivo* and the prevention of cell death by apoptosis with pharmacological knowledge are possibilities requiring well-developed safety assessment.

Myocardial cell damage in ischemia is mediated by the interplay of several mechanisms at the cellular and individual level. Three basic cellular mechanisms are oxidative stress, apoptosis, and inflammation. All three play a role in ischemia and reperfusion. But the major contribution of inflammation comes into play after reperfusion as described in the following sections.

Oxidative stress

Oxidative stress is more often associated with elevated levels of reactive oxygen species (ROS) or reactive nitrogen species (RNS) in the cellular and subcellular levels [9]. However, ROS/RNS at suboptimal levels can act as signaling molecules in maintaining the cardiovascular function [10]. On the other hand, increased ROS/RNS levels can induce pathology by damaging lipids, proteins, and DNA [11]. These free radicals also attract polymorphs, further aggravating neutrophil-induced damage [12], [13]. Another mechanism of myocardial damage is by apoptosis induction [15]. ROS production in mitochondria on reperfusion may cause mPTP opening that leads to apoptosis as illustrated in Figure 1. Thus, ROS, depending on their concentration, site of production, and the overall redox equilibrium of the cell, will determine their biological action (beneficial or deleterious) in the tissues. Cardiovascular pathology associated with oxidative stress is observed in several cardiac diseases such as IRI [16], [17]. Mitochondrial antioxidants have proven to be protective in animal models [18]. Platelet-derived MVs also act by decreasing oxidative stress [7].

Figure 1: Sources of ROS in mitochondria and mPTP opening upon reperfusion.[19].

Mitochondrial ROS are generated by leakage of electrons from the electron transport chain, causing the incomplete reduction of oxygen to superoxide anion ($O_2^{\bullet-}$). In particular, succinate-driven RET leads to mitochondrial matrix superoxide production from complex I early during reperfusion. Mitochondrial NOX₄ also contributes to H₂O₂ generation. mPTP formation is inhibited by acidosis and promoted by calcium and ROS [19]. Reprinted from *Free Radical Biology and Medicine*, Vol. 117, Cadenas S, ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection 76–89, Copyright (2018), with permission from Elsevier.

Apoptosis

Myocardial ischemia leads to the release of various cytosolic components, which are detected by molecules of the immune system, e.g. toll-like receptors (TLRs) and nod-like receptors (NLRs). These in turn activate a complex inflammatory reaction called ‘inflammasome’, which results in the activation of the caspase cascade and cytokine release, culminating in cell death [20], [21]. IRI further amplifies these responses by various mechanisms [22], [23], [24], [25]. Inhibition of apoptosis can limit the loss of myocardial cells [26], [27]. Drugs known to have favorable effects in ischemic cardiomyopathy, including angiotensin converting enzyme inhibitors, angiotensin II antagonists, and beta blockers, have shown anti-apoptotic effects in animal models. They do this through the inhibition of the renin-angiotensin system and sympathetic nervous system, which are effectors that, under certain conditions, can trigger apoptosis [28], [29], [30]. Antioxidants can act as anti-apoptotic substances because oxidative stress and the generation of ROS may trigger ‘intrinsic’ apoptosis. In a mouse model of ischemia-reperfusion, in fact, the antioxidant was able to prevent the overexpression of various pro-apoptotic molecules [31]. Potential targets to prevent apoptosis include caspases and endonuclease [32], [33], [34]. Inhibitors of these enzymes were found to be capable of reducing infarct and left ventricular remodeling in experimental models of ischemia-reperfusion damage [31]. One animal study reported that apoptosis was induced only by reperfusion [35].

Insulin-like growth factor is an example of an inhibitor of caspase-3 showing anti-apoptotic effect, which can improve heart function in animal models of cardiomyopathy [36], [37]. However, there are some limitations of the therapeutic strategies aimed at inhibiting apoptosis in clinical practice, especially regarding the carcinogenic potential of such interventions. Furthermore, while in animal models the time and doses of anti-apoptotic drugs are well controlled, there is no well-defined reference to their application in clinical practice.

Inflammation and activation of the complement system

Restoration of the coronary blood flow triggers an inflammatory response. This inflammatory damage during reperfusion is primarily caused by a massive circulating neutrophil invoked in the reperfused area by the cytokines IL-1ra, IL-6, IL-8, and IL-10, complement activation and adhesive molecules expressed by endothelial and parenchymal cells [19], [38], [39], [40], as well as by the release of cytosolic components from necrotic cells. Complement components play a vital role in IRI by mediating neutrophil adherence to endothelial cells [41], [42], [43] and inducing apoptosis [43]. However, complement activation is also noted in the absence of reperfusion [44], and anti-complement therapies have failed to improve the post-perfusion infarct size [45], [46], making the role of the complement controversial. The recruited neutrophils secrete cytokines and different proteolytic enzymes, leading to lethal tissue damage in the reperfused area [47]; neutrophil accumulation and response is also observed in MI without reperfusion, but this response is accentuated with reperfusion and is reported to be associated with increased size of infarct [13], [48], [49]. The extent of the cellular damage also depends on additional circumstances, including the duration of blood flow interruption particularly in myocardial tissues, the degree of response to the more or less optimal treatment, and the probability of the individual patient survival [50]. Chang et al. studied the role of these and many other clinical factors on post-resuscitation myocardial function [51]. Adrie et al. compared the blood immunochemistry levels in patients who suffered cardiac arrest after resuscitation. Their results showed raised cytokines, cytotoxin, and TNF receptors. IL-6 was 20 times higher in nonsurvivors compared to survivors [52]. Another study reported levels about 50 times exceeding those under physiological values [53]. The increased level of IL-6, TNF- α , and endothelin cause vasoconstriction and facilitate neutrophil and platelet adhesion to the endothelium, enhance chemotaxis that leads to systemic abnormalities of vascular function. Some IgM antibodies, for unknown reasons, tend to be deposited in ischemic tissue when blood flow is restored. The complement fractions bind to these antibodies that are activated and induce further cellular damage and increased inflammatory reaction [54].

Pharmacological targets for known ischemia-reperfusion injury mechanisms

The pharmacological cardioprotective strategy to prevent acute global IRI has been tested using different approaches. Over the last few years, multiple pharmacological agents, including volatile anesthetic agents [55], [56], [57], sodium hydrogen exchange inhibitors [58] and statins [59], [60], [61], pharmacological preconditioning [62], [63], anti-oxidants [64], [65], anti-platelets [6], and anti-inflammatory strategies [66], [67], have been explored as potential cardioprotective therapies. However, most preclinical strategies showing cardioprotective effects did not work in clinical settings [68].

Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P) present in the plasma is mainly produced by endothelial cells, platelets, erythrocytes [6], and hepatocytes; other sources include platelets, mast cells, endothelial cells, fibroblasts, and the central nervous system [69], [70], [71], [72]. It is a bioactive lysophospholipid (LP) derived from sphingomyelin and ubiquitous in lipid cell membranes [70] having wide function from apoptosis (pro-apoptotic) to protective (anti-apoptotic) as shown in Figure 2. Sphingosine is formed by the enzyme sphingosine kinase. S1P performs its functions by binding to five G-protein receptors (S1P1, S1P2, S1P3, S1P4, and S1P5) [73]. Recently, researchers have discovered that P2Y12 receptor antagonists, a group of antiplatelet drugs, exert their cardioprotective effect by interacting with some factor in platelets to activate sphingosine kinase [6]. This effect is independent of their anti-thrombotic effect.

Figure 2: Interconversion of sphingolipids, including the formation of S1P, from sphingosine.

The effects of pro-apoptotic ceramide are countered by S1P, which is generally a survival signal [74]. Reprinted from Current Opinion in Pharmacology, Vol 9, issue 2, Simon Kennedy, Kathleen A Kane, Nigel J Pyne, Susan Pyne, Targeting sphingosine-1-phosphate signalling for cardioprotection, Pages No.194-201, Copyright (2009), with permission from Elsevier.

Among the many effects are cytoprotective antioxidant, immunosuppressive effects [75], and its possible role in reducing ischemia-reperfusion [76]. Recent studies have shown that S1P reduces IRI in the liver [77], kidney [78], and brain [79]. S1P is also able to increase the survival of cardiomyocytes during episodes of hypoxia, whose evidence emerged from *in vitro* studies [80], [81]. It can also reduce the size of the infarcted area in productions of isolated hearts *ex vivo* [82], [83].

S1P mediates different physiological functions [84], including cell proliferation, differentiation, and survival, as well as the reorganization of the cytoskeleton, formation of cytoplasmic extensions, cell motility and chemotaxis, intercellular adhesion, and formation of the junctions between cells. It is also involved in maintaining immunity, pulmonary vascular smooth-muscle tone, and endothelial barrier integrity.

Effects of fingolimod

Fingolimod has generally been proven to be safe and well tolerated. However, it has presented adverse events of medium to moderate severity, including sinus bradycardia, atrioventricular block, infections, increased liver enzymes, hypertension, and macular edema.

Cardiovascular effects still constitute a major source of concern in the clinical setting, especially after the administration of the first dose of the medicine [85]. These effects have been evaluated through four Phase IV clinical trials: TRANSFORMS, FREEDOMS, FREEDOMS II, and FIRST [86], [87], [88], [89], [90], [91]. These studies have reported that the effect of the drug in reducing heart rate is similar in patients with and without cardiovascular risk factors. Bradycardia induced by the standard FDA-approved dose of 0.5 mg/day was transient, asymptomatic, or caused mild symptoms, but did not require any treatment; it was observed after the first dose but returned to baseline after about a month, despite treatment continuation [92]. Bradycardia and heart block observed at the dosage of 1.25 mg/day required treatment only in two patients [92]; this high dose is not approved by the FDA. Associated symptoms are rare, transient, and usually without clinical consequences. A recent multicenter Phase IV trial (EPOC) confirmed these findings [93].

Cardioprotective mechanism of fingolimod

Several mechanisms have been claimed to contribute to the cardioprotective effects of fingolimod: by reducing oxidative stress and apoptotic effects, inhibiting inflammatory mediators, and reducing the loss of cardiomyocytes in hypoxic conditions [94], [95], [96]. The new therapeutic perspectives of fingolimod result from increasing knowledge on S1P [70], [97]. S1P on cardiomyocytes binds to the G-protein coupled receptors S1PR1 and S1PR3, leading to the activation of numerous intracellular signal transduction pathways involved in cardioprotective action. S1PR1, in particular, is the main receptor of S1P in cardiomyocytes and typically activates the RISK (reperfusion injury salvage kinase) and SAFE (surviving activating factor enhancement) signal transduction pathways [76], [94], [98]. These pathways mediate the cardioprotective effects of fingolimod. They act through the prevention of apoptosis and oxidative stress actions that contribute to the larger size of the infarct [99], [100], [101]. These pathways are the main molecular cascades that can inhibit mitochondrial transition pore openings [102], [103], [104], [105], and previous *in vitro* studies claim that S1P can activate these pathways as demonstrated in Figure 3.

In addition to the aforementioned significance of S1P in the activation of the RISK and SAFE pathways, the downstream pathway S1P-R is a potential therapeutic target to prevent peri-infarct. Evidence arising from previous preclinical studies suggests that S1P represents a very promising pharmacological target for mitigating the damage from myocardial ischemia-reperfusion. In ventricular cardiomyocytes of rats [80], [81], S1P increased cardiomyocyte survival during episodes of hypoxia. It is also reported to induce resistance to IRI in rat hearts *ex vivo* [82], [83]. Another piece of evidence for its cardioprotective effects is the development of greater ischemia-reperfusion myocardial damage in the hearts of mice lacking the enzyme sphingosine kinase, an enzyme necessary for the synthesis of S1P [106], [107]. The role of S1P on the size of the myocardial damage is confirmed, as S1P receptor knockout mice show an area of larger infarct compared to controls [108], [109].

S1P not only reduces myocardial damage but also provides cardioprotection by the metabolism of sphingosine, which also seems to be a key mediator in pre-conditioning and post-conditioning [110]. In fact, both pre- and post-conditioning can reduce the size of the infarct, which does not take place in hearts lacking sphingosine kinase or S1P receptors [83], [106], [107], [109]. The mitochondrial transition pore opening represents the final step that leads to apoptosis of cardiomyocytes in IRI and is able to trigger oxidative stress that characterizes it. Therefore, preventing the mitochondrial transition pore opening can reduce the infarct size [111], [112].

Previous studies have shown the great benefits of immunosuppression in the prevention of IRI [113]. This function is the basis of fingolimod use for treating multiple sclerosis (MS). It also exerts an immunomodulatory action by sequestering the lymphocytes from peripheral blood and tissues to the lymph nodes and reducing the lymphocyte output from the lymph nodes themselves [70], [114].

Wang et al. observed that in mice with spontaneous coronary artery occlusion, fingolimod reduced the size of the infarcted area (*ex vivo*) as well as mortality [90]. In addition, it also reduced count of CD4 and CD8 T cells and increased the number of T regulatory cells, suggesting the contribution of immunosuppressive effects of fingolimod to its cardioprotective properties. Together, these findings emphasize that S1P and its synthetic analog fingolimod may have a role in the prevention of IRI.

Figure 3: Sphingosine-1-phosphate signaling pathways [115].

(a) The multistep production of sphingosine-1-phosphate (S1P) is governed by several enzymes, including sphingomyelinase, ceramidase and sphingosine kinase (SphK). (b) Ceramidase converts ceramide (Cer) into sphingosine (Sph), which is later phosphorylated by SphK into S1P. Cer leads to the activation of caspase-3 (cap3), resulting in apoptosis, while S1P can also be transported to the extracellular milieu, where it acts in an autocrine or paracrine fashion by binding the S1P receptor (S1PR) and activating phosphoinositide 3-kinase (PI3K) and AKT, leading to cell survival. (c) Binding of S1P to its receptor initiates several downstream signaling pathways via coupling to respective G-proteins. Cartoon diagrams of S1PR1–5 were generated using PyMOL. All protein structures except S1PR1 were modeled using MODELLER 9.13S1PR2, S1PR3, S1PR4 and S1PR5 protein models were generated using the template structure of the S1PR1 (Protein Data Bank id: 3V2W). Transmembrane helices of different receptors are shown in different colors to differentiate them in the membrane. Abbreviations: ERK, extracellular signal-regulated kinase; PKC, protein kinase C; PLC, phospholipase C. [115]. Reprinted from Drug Discovery Today, Vol. 21, Arish M, Husein A, Kashif M, Saleem M, Akhter Y, Rub A, Sphingosine-1-phosphate signaling: unraveling its role as a drug target against infectious diseases, page no. 133–42. Copyright (2016), under the terms of Creative Common Attribution License.

Along with its cardioprotective effects, studies on isolated rat hearts have shown that fingolimod also reduces IRI and improves myocardial function [96]. Despite these different confirmations about the various cardioprotective effects, they have not yet been studied in models of large animals and humans.

To further investigate the drug's role in reducing IRI, a study was carried out by Santos-Gallego et al. in a model of myocardial ischemia-reperfusion in pigs, including a short-term protocol (fingolimod administration 15 min before reperfusion in the study group vs saline in controls) and a long-term protocol (fingolimod 15 min before reperfusion vs saline in controls; the same treatment repeated once a day for 3 days) [116]. The fingolimod group showed a significant reduction of cardiomyocyte apoptosis [98] in the periphery of ischemic myocardium, resulting in decreased infarct size as compared to controls. It was quantified by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL). The drug also improved the long-term remodeling of heart in addition to these short-term effects. These cardioprotective effects may be attributable to its action as an antioxidant [75], [117], as it decreased the concentration of 8-hydroxydeoxyguanosine, which is a marker of oxidative stress, and increased the levels of the antioxidant superoxide dismutase's enzyme activity [116].

Activation of RISK and SAFE pathways

Fingolimod reduces cardiomyocyte apoptosis through the activation of the signal transduction pathways RISK [105] and SAFE [118]. Confirming this, the administration of Wortmannin, an inhibitor of the RISK pathway

(including Akt/ERK/GSK-3 β), or the simultaneous administration of AG490, a SAFE pathway inhibitor (Janus kinase/STAT3), obliterated the drug's anti-apoptotic effect in myocardial tissue [116]. It has been demonstrated that Akt1/2, GSK-3, ERK1/2, and p-STAT-3 were significantly increased in the ischemic myocardial tissue in fingolimod-treated animals, reflecting the cardioprotective effect. Santos-Gallego et al. [116] reported how fingolimod activated Akt1/2, ERK1/2, STAT3- β , and GSK3 phosphorylation 24 h after MI [119], [120]. Russo et al. reported that S1P released from platelets plays an important role in protecting the heart by stimulating the ERK, PI3K, and PKC pathways [121].

In addition to promoting the survival pathways Akt1/2 and ERK1/2 [122], fingolimod is also important for the growth of heart cells. Their short-term activation decreases apoptosis, but their continued activation for longer periods causes cardiomyocyte hypertrophy, which is one of the key features of left ventricular remodeling [123], [124], which negatively impacts cardiac health. But, fingolimod reduced the activation of these receptors in the long run, resulting in reduced remodeling [116]. The anti-apoptotic effect of fingolimod is proven in the literature by the decreased activation of the pro-apoptotic markers p53 and caspase-3 [119], [125] and enhanced expression of anti-apoptotic markers including Bcl-2 and kinase C- ϵ in fingolimod-treated animals. This anti-apoptotic pathway activation using fingolimod indicates significant reduction in the size of MI area.

Role of fingolimod on ischemic cardiomyopathy

According to the literature, fingolimod has the potential to reduce the infarcted area, thus leading to the preservation of left ventricular function. This finding has been reported by Santos-Gallego et al., who demonstrated improved ventricular function by cardiac magnetic resonance at early and late phases, where better function (contractility) was preserved in the fingolimod-treated group [116]. Both improved LVEF (left ventricular ejection fraction, and the presence of proper contractile reserve indicated favorable outcomes [126], [127]. Fingolimod also plays important role in post-MI structural remodeling, which is a harbinger of ischemic cardiomyopathy in the long run [116]. Remodeling is characterized by dilation, compensatory hypertrophy, and changes in left ventricular sphericity. Fingolimod attenuated left ventricular tissue remodeling after MI at 1 week in one group and after 1 month in another, which was also confirmed by measuring the ventricular wall thickness by echocardiography [116].

The anti-remodeling effect is also confirmed at the histological level, as demonstrated by reduced collagen deposition in the myocardial interstitium and smaller cardiomyocytes in the fingolimod-treated group [98]. The attenuation of anatomical remodeling is also supported by lower neurohormonal activation, indicated by reduced levels of aldosterone and blood metanephrines. These findings emphasize that the fingolimod group is in harmony with the best anatomical left ventricle level outcomes.

Conclusion

This review has identified a pharmacological agent that can protect the myocardium from ischemia and reperfusion damage by using fingolimod pre- and post-conditioning. It works by decreasing the oxidative stress, apoptosis, and inhibiting the inflammatory cascades in addition to other signalling pathways in myocardial ischemia reperfusion injury in clinical practice. Translation of studies published on cardioprotective role of fingolimod (FTY720) in experimental models will open new avenues to protect heart during myocardial ischemia and reperfusion.

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