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Review

Multidrug prevention or therapy of ischemia-reperfusion injury of the heart—Mini-review

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ABSTRACT

Restoration of blood flow to myocardium previously subjected to ischemia leads to ischemia/reperfusion injury due to oxidative stress. An increased production of toxic peroxynitrite, an enhanced phosphorylation and nitration/nitrosylation of myocyte contractile proteins and overactivation of matrix metalloproteinases – are only one of the several causes of heart damage. Multifactorial basis of ischemia/reperfusion injury demands the use of multiple pharmacological agents, inhibiting several pathways of cardiac injury. Nevertheless, the use of these drugs in their therapeutic doses, apart from their role in the treatment of pathological events, may also disturb physiological processes leading to numerous side-effects. Therefore current preclinical studies focuses on multidrug therapies in their low concentration. Synergistic or additive effect of low multidrug therapy inhibit pathological processes while maintaining the proper cell function and avoid alteration of physiological role of important functional proteins. This study provides information about multidrug strategies for the prevention/treatment of cardiac injury induced by oxidative stress.

1. Introduction and background

Pharmacological or mechanical coronary reperfusion has become the standard procedure for the treatment of acute myocardial infarction (MI) for more than 20 years (Byrne et al., 2003). However, restoration of blood flow to myocardium previously subjected to ischemia leads to ischemia/reperfusion (I/R) injury. Pathomechanism of I/R injury is a complex and multifactorial issue leading to numerous metabolic, morphological and contractile disorders in the myocardium (Cadete et al., 2013b; Doroszko et al., 2009; Polewicz et al., 2011). Neutrophil infiltration at the site of heart injury and an increased formation of oxygen radicals (ROS) in the area of I/R (Byrne et al., 2003; Murphy and Steenbergen, 2008) lead to DNA damage, mitochondrial malfunction, damage of cell membrane and consequently to cell death. This imbalance between the formation and neutralization of pro-oxidants leads to phenomenon referred to as “oxidative stress”. Oxidative stress triggers in turn in an increased expression of inducible or endothelial NO synthases (iNOS and eNOS), subsequent production of toxic peroxynitrite (ONOO–), enhanced activation of matrix metalloproteinases (MMPs) and consequently to heart damage (Jacob-Ferreira and Schulz, 2013). It has also been shown that oxidative stress induces phosphorylation and nitration/nitrosylation of myocardial contractile proteins, such as myosin light chain 1 and 2 (MLC1 and MLC2), titin and TnI, its MMP-2 mediated degradation and contractile dysfunction (Ali et al., 2010; Cadete et al., 2012; Doroszko et al., 2009; Lin et al., 2014; Polewicz et al., 2011). On the basis of these evidences, agents that reduce the extent of myocardial injury in clinical or experimental studies were tested. Some of pharmacological strategies involved: a cell membrane receptor agonist adenosine, angiotensin-converting enzyme inhibitors, opioids and erythropoietin, antioxidant activity and vasorelaxing effects of phenolic compounds or the mixed cell membrane and intracellular agonists (Gross and Gross, 2007). Currently, aspirin and/or β-blockers are administered for most of patients with suspicion of acute MI (Rosamond et al., 2008). The challenge of multidrug therapy is to provide a maximum benefit with a minimum of side effects: the adverse drug reactions, drug-disease and drug-drug interaction (including both prescription and over-the-counter preparations). Moreover, a personalized therapy with drug mixture may require the assessment of an individual doses of each drug.

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2. Pharmacological prevention and treatment of injured heart

As no current pharmacological agent alone is capable to prevent I/R injury, the new directions in pharmacological prevention and treatment of injured heart is still developing. It was documented that heart failure, also due to MI, is associated with multiple myocardial metabolic remodeling causing changes in cardiomyocytes, endothelium, vascular smooth muscle cells as well as interstitial cells and matrix (Heusch et al., 2014). Ischemic heart disease alters energy substrate metabolism in myocytes. During ischemia, decreased oxygen supply leads to significant increase of mitochondrial glucose oxidative metabolism and glycolysis became a leading way for energy production (Lopaschuk, 2006). These in turn can lead to intensive accumulation of lactate due to enhanced anaerobic glycolysis, predominant fatty acids oxidation and harmful acidosis of myocytes. Moreover, an enhanced fatty acid oxidation as a source for the generation of ATP during I/R has a negative impact on cardiac efficiency and contractile function (Lopaschuk, 2006). Hence optimizing of myocyte energy substrate metabolism by manipulation of the activity of enzymes involved in fatty acids and glucose metabolism became an important target for therapeutic intervention. Some studies described therapeutics targeting heart metabolism such as: trimetazidine which inhibits the terminal enzyme of fatty acid oxidation and myocyte apoptosis (Lopatin et al., 2016), dichloroacetate which inhibits the activity of pyruvate dehydrogenase kinase, and thus stimulates glucose oxidation (Azam et al., 2015), inhibitor of carnitine palmitoyl transferase-I, that shift the energy substrate metabolism from fatty acids oxidation to glucose oxidation (Lee et al., 2005). Other sources described β-blockers, which reduce neurohormonal activation and catecholamine-induced lipolysis, and hence circulating plasma fatty acid concentrations, inhibitors of 3-ketoacyl-coenzyme A thiolase, and fibrates which through decreasing circulating fatty acids, decrease its oxidation in myocardium (Wayman et al., 2002). Another concept suggested the promotion of glycolysis and reduction of circulating fatty acids by use of GIK (glucose-insulin-potassium) solution, which improved post-ischemic recovery of heart contractile function (Zhang et al., 2006). Although optimization of the balance between fatty acid and glucose metabolism results in an improvement of cardiac mechanical function after I/R, the practical implementation of these therapeutic agents in prevention or therapy of MI injury is limited due to some side effects, limited effectiveness on survival and clinical course (Ceremuzyński et al., 1999). In summary, multifactorial basis of I/R injury, including intracellular proteolytic degradation, posttranslational modifications of contractile and functional proteins as well as metabolic changes affecting myocyte contractility demand the use of multiple pharmacological agents, inhibiting several pathways of cardiac injury. Nevertheless, the use of drugs in their therapeutic doses, especially those which non-selectively affects their targets, apart from their role in the treatment of pathological events, may also disturb physiological processes leading to numerous side-effects. Cardiac cytotoxicity is observed with the currently available MMP-2 and kinase inhibiting drugs when higher doses are used (Castoldi et al., 2007). Moreover, MMP-2 which has been shown to be necessary for regulation of MLC levels under physiological conditions, but is also overactive to MLC1 after its ROS dependent modifications (Doroszko et al., 2009; Lin et al., 2014). Moreover, posttranslational modifications (PTMs) of MLCs are also important for physiological processes, such as vascular aging and regulation of heart contractility (Steinberg, 2013). Apart from cardiomyocytes, fatty acid are the main source of fuel for other tissues in normal aerobic condition and play an important role in intracellular signaling and production of prostaglandins. For this reason, full pharmacological blockade of MMP-2 activity, PTMs of MLCs and fatty acids oxidation would result in a multitude of side-effects that may be as detrimental as oxidative stress induced injury itself. Moreover, full doses of drugs exhibit a cytotoxic effect affecting cell structure and function. Hence current preclinical studies on the prevention or therapy of I/R injury focuses on low-dose multidrug therapies (instead of one drug at a therapeutic concentration) which through synergistic or additive effect allow to reduce overactivation of important functional proteins while avoiding alteration of their physiological role and maintaining the proper cell function. This review provides structured information about multidrug strategies for the prevention and treatment of cardiac injury induced by oxidative stress.

3. Proteolytic enzymes as a target for multidrug therapy

One of several pharmacological targets for the prevention/therapy of I/R injury is a group of matrix metalloproteinases (MMPs). MMPs are a family of more than 25endopeptidases, which play an important role in a variety of physiological processes including morphogenesis, cartilage and bone repair, wound healing, cell migration and angiogenesis (Sawicki et al., 1997). The main targets for MMPs proteolytic activity are collagen, gelatin and elastin, hence MMPs specifically degrade extracellular proteins leading to disintegration and remodeling of the different segments of extracellular matrix (ECM) (Singh et al., 2015). MMP-2 is the most ubiquitous member of MMPs family, and is expressed in cells of the heart and vasculature (Ali et al., 2011). MMPs have also been recognized to be significant contributors to cardiac pathologies including congestive heart failure, acute MI, dilated cardiomyopathy, peroxynitrite-induced contractile dysfunction, atherosclerosis, restenosis, and heart failure (Kwan et al., 2004; Sawicki et al., 1997). Apart from the role of MMP-2 in the degradation of ECM, there is a clear evidence for its intracellular localization to the cardiac sarcomere, which contributes to proteolysis of specific sarcomere and cytoskeletal proteins (Ali et al., 2011). The studies on MMP-2 at the cellular level revealed that rapid activation of MMP-2 within second to minutes following I/R contributes to degradation of big-endothelin (Cheung et al., 2000). It has also been shown that the action of MMP-2 includes the intracellular degradation of tinin (Ali et al., 2010), desmin (Sung et al., 2007), poly (ADP-ribose) polymerase in the nucleus (Kwan et al., 2004), and sarcomere proteins such as α-actin (44), TnI (Wang et al., 2002b) and MLC1/MLC2 (Sawicki et al., 2005), leading to contractile dysfunction of cardiomyocytes (Haase et al., 2006). The discovery that MMP-2 may act at a cellular level has established a new direction for the study of its role in cardiovascular disease. MMP activity may be regulated at multiple levels including transcription, modulation of mRNA half-life, secretion, localization, activation or suppression by specific and nonspecific proteinase inhibitors (Lin et al., 2014). MMPs are released to ECM in inactive stage of proenzymes. The activation of MMPs is achieved by proteolytic cleavage of the N-terminal propeptide by a membrane-type MMP or its chemical modifications by ROS, such as the S-glutathiolation of autoinhibitory domain of proMMPs or nitration of proMMPs. Proteolytic removal of the propeptide region perturbs the binding of a key cysteine thiol residue with the active Zn site. The disruption of this Cys-Zn^{2+} bond can be also induced by ONOO–, hence oxidative stress may directly activate MMPs. MMPs are naturally regulated by the endogenous tissue inhibitors of metalloproteinases (TIMPs), but interestingly, TIMPs are readily inactivated by peroxynitrite, which suggests that peroxynitrite may potentiate MMP activity not only by direct activation of proMMPs but also by preservation of MMP activity after it is generated.

Naturally-occurring polyphenolic compounds (e.g. flavonoids) have shown myocardial protective effects via antioxidant potential, preservation of nitric oxide, anti-inflammatory activities and ability to inhibit MMP activity. The inhibition of MMP by flavonoids occur through the transcription factors activator protein-1 (AP-1) and nuclear factor-kappaB or by stimulation of the expression of TIMP-1 in human vascular endothelial cells treated with oxidized LDL (Lee and Moon, 2005). Moreover, since doses of polyphenols inhibit MMP activity and prevent angiogenesis, low doses of polyphenols show angiogenic effects without altering activity of MMP (Baron-Menguy et al., 2007). This unique dual effect of polyphenols might be useful during composing of