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Redox signaling in remote ischemic preconditioning-induced cardioprotection: Evidences and mechanisms

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ABSTRACT

Reactive oxygen species are the reactive molecules that are derived from molecular oxygen and play an important role as redox signaling molecules to confer cardioprotection. Various scientists have demonstrated the key role of redox signaling in cardioprotection by showing a transient increase in their levels during remote ischemic preconditioning (RIPC) phase. The transient increase in reactive oxygen species levels during remote preconditioning phase may take place either through activation of K_{ATP} channels or through increased nitric oxide (NO) production. A transient increase in reactive oxygen species during preconditioning may also increase the expression of heat shock proteins (HSP), the level of antioxidant enzymes and decrease the expression of inflammatory genes (Egr-1) during ischemia-reperfusion phase to confer cardioprotection. The present review describes the role of redox signaling in RIPC-induced cardioprotective effect with possible mechanisms.

1. Introduction

Remote ischemic preconditioning (RIPC) is the non invasive technique in which transient, repeated, interspersed episodes of ischemia and reperfusion applied to remote organ, renders the myocardium resistant against sustained ischemic insult (Randhawa and Jaggi, 2016a, 2016b; Przyklenk and Whittaker, 2011; Anttila et al., 2016). Apart from preclinical studies, there have been clinical studies documenting that RIPC alleviates ischemia-reperfusion injury in patients undergoining angioplasty, percutaneous coronary intervention and coronary artery bypass surgery (Przyklenk and Whittaker, 2011; Thielmann et al., 2013).

Redox signaling is a process of reversible oxidation and reduction of cellular signaling components of the body by reactive oxygen species including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH^-) (Buresh and Berg, 2015; Forman et al., 2004). Reactive oxygen species are well documented to induce oxidative stress and are involved in pathophysiology of various diseases like hemorrahgic shock (Guarini et al., 1996), renal injury (Zhu et al., 2016), cardiovascular disease (Boaz et al., 2000), cardiac arrest (Ottani et al., 2014), tissue necrosis and reperfusion injury (Granger and Kvietys, 2015; Ottani et al., 2013), inflammatory bowel disease (Biasi et al., 2013) and cancer (Sies, 2015). However, apart from deleterious effects of free radicals, ample studies have shown that redox signaling also confers protective and physiological functions (Deng et al., 2012; Shkolnik et al., 2011; Mittler, 2017). In ischemic preconditioning, redox signaling act as a trigger, particularly during early reperfusion phase rather than ischemic phase (Dost et al., 2008) to induce cardioprotective effect (Otani, 2004).

Studies have also shown that RIPC also triggers redox signaling pathway, in which transient increase in reactive oxygen species during preconditioning phase confers cardioprotection (Chen et al., 2005; Khanna et al., 2008; Shahid et al., 2008). Reactive oxygen species produces its cardioprotective effect through various pathways like, increase in HSP expression (Chen et al., 2005; Madamanchi et al., 2001) and decrease in Egr-1 gene level (Mudaliar et al., 2017). The present review describes the cardioprotective effects conferred by redox signaling during RIPC with possible mechanisms.

2. RIPC triggers reactive oxygen species generation during preconditioning phase

There have been studies suggesting an increase in free radicals production during remote preconditioning phase, which may trigger redox signaling to confer cardioprotection (Chen et al., 2005; Weinbrenner et al., 2004; Khanna et al., 2008; Shahid et al., 2008). Chen et al. demonstrated that remote preconditioning in rats with repeated four cycles of ischemia-reperfusion of the femoral artery attenuated sustained ischemia-reperfusion-induced injury in in vivo model of coronary artery ligation (performed after 2 h of preconditioning in rats) in terms of reduction in infarct size (TTC stain method). Furthermore, RIPC also increased the production of reactive oxygen

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species, which was observed in blood at different time point by chemiluminescence method. The level of reactive oxygen species were significantly elevated after 2 h of RIPC *i.e* before coronary artery ligation. Moreover, administration of N-(2-mercaptopropionyl)-glycine, a free radical scavenger, attenuated cardioprotective effect of RIPC suggesting that production of free radicals during preconditioning phase may be responsible for cardioprotective effect (Chen et al., 2005).

Our own study demonstrated that administration of N-acetyl cysteine (NAC), a free radical scavenger, attuenuated the cardioprotective effects of remote aortic preconditioning, again emphasising that generation of free radicals during preconditioning phase may trigger redox signaling to produce cardioprotection (Khanna et al., 2008). A study of Shahid et al. demonstrated the important role of reactive oxygen species in RIPC-induced cardioprotection. Remote hind limb preconditioning in the form of occlusion of femoral arteries of rats for 15 min followed by 10 min of reperfusion before left anterior descending coronary artery occlusion was shown to attenuate ischemic injury. However, RIPC-induced protection was blocked in the presence of N-acetyl cysteine, a reactive oxygen species scavenger, suggesting the role of reactive oxygen species in RIPC-induced cardioprotection (Shahid et al., 2008). NADPH oxidase is an important enzyme, involved in the production of reactive oxygen species (Kuwabara et al., 2015). Recently, it has been shown that remote preconditioning stimulus increases the expression of NADPH oxidase (NOX 2) in rat hearts suggesting that NADPH oxidase mediated increase in reactive oxygen species may mediate cardioprotection (Mudaliar et al., 2017).

An earlier study of Weinbrenner et al. also demonstrated the role of redox signaling in RIPC induced cardioprotection. Remote preconditioning with infrarenal occlusion of the aorta in rats for 15 min, followed by 10 min of reperfusion period was shown to attenuate infarction of heart produced by 30 min of regional ischemia, followed by 30 min of reperfusion. Administration of N-(2-mercaptopropionyl)-glycine blocked a single preconditioning cycle-induced cardioprotection, suggesting that mild preconditioning stimulus (single cycle) induced protection is dependent on free radical generation. However, there was no influence of N-(2-mercaptopropionyl)-glycine in strong preconditioning stimuli (3 cycles of preconditioning) induced cardioprotection, suggesting that during strong preconditioning stimulus, there may be an involvement of mediators other than free radicals (Weinbrenner et al., 2004).

3. RIPC decreases reactive oxygen species and increases antioxidant enzymes during ischemic phase

There have been evidences suggesting that RIPC decreases the levels of reactive oxygen species and increases the levels of antioxidant enzymes during ischemic reperfusion phase. A study of Konstantinov et al. (2005) demonstrated that RIPC increases the expression of genes involved in protection against reactive oxygen species (Hadhsc, Prdx4 and Fabp4). Chen et al. reported a significant increase in levels of antioxidant enzymes (Mn superoxidase dismutase, glutathione peroxidase) in the area at risk portion of heart in response to RIPC. However, there was no difference in expression of both enzymes with N-(2-mercaptopropionyl)-glycine treatment. In other words, N-(2-mercaptopropionyl)-glycine did not alter RIPC-induced increase in antioxidant enzyme levels (Chen et al., 2005). Rassaf et al. (2014) demonstrated that four cycles of remote hind limb preconditioning (5 min ischemia-5 min reperfusion) by femoral artery occlusion significantly attenuated sustained ischemia-reperfusion associated increase in free radical production in mice. A recent study of Mudaliar et al. (2017) demonstrated the RIPC stimulus decreases the production of H_2O_2 in a culture media of cardiac myoblasts H9c2 cells, in response to hypoxia-reperfusion. Although, there is a close relationship between reactive oxygen species levels and tissue protection, yet, it should be clear that reduction in reactive oxygen species levels during ischemic phase does not necessarily mean treatment of disease. It might be possible that treatment of disease may itself decrease reactive oxygen species levels in heart.

4. Mechanisms involved in redox signaling–induced cardioprotection in RIPC

4.1. Heat Shock Proteins (HSP)

Heat shock proteins (also known as chaperones) are stress proteins, which are classified on the basis of molecular weight and these play an important role in cell-cycle control, folding, defolding and assembling of protein complexes (Nakai and Ishikawa, 2001). There have been a number of studies suggesting that the upregulation of HSP is associated with cardioprotection (Jimenez et al., 2014; Wei et al., 2006). An infection with replication deficient adenovirus encoding for HSP 70 and HSP 27 before myocardial infarction has been shown to increase the HSP 70 and HSP 27 levels and produce protection (Wei et al., 2006). Chen et al. proposed that RIPC-induced activation of redox signaling may upregulate these heat shock proteins to confer cardioprotection. The authors demonstrated that along with the rise in reactive oxygen species levels, there was a significant increase in the levels of heat shock proteins (HSP 70, HSP 25) in the area at risk in heart in response to RIPC. Furthermore, treatment with free radical scavenger reduced the levels of HSP 70 and HSP 25, and also attenuated RIPC-induced cardioprotection (Chen et al., 2005). It probably suggests that during remote preconditioning, an increase in free radical production may trigger the production of heat shock protein that inturn may confer resistance to myocardium against sustained ischemia reperfusion injury. An earlier study has also shown that upregulation of heat shock protein may be secondary to increase in reactive oxygen species. Pretreatment with H_2O_2 (2000 μg mol/L), (as reactive oxygen species), has been shown to increase the expression of HSP in vascular smooth muscle cells (Madamanchi et al., 2001). Another study has also shown that oxidative stress may induce the production of heat shock proteins (Omar and Pappolla, 1993).

In contrast, there have been studies showing that heat shock proteins may stimulate the production of reactive oxygen species (Baruah et al., 2014; Multhoff et al., 2015). Therefore, it may not be ruled out that RIPC triggers heat shock protein production, which inturn may activate reactive oxygen species production and confer cardioprotection. However, more studies are required to fully elucidate the possible interaction between heat shock protein and free radicals during RIPC-induced cardioprotection.

4.2. Egr-1 gene

Egr-1, also known as Zif268, is an early growth response gene (immediate master regulator gene), and plays a critical role in pathogenesis of diseases, such as cancers, tumors, ischemic-reperfusion injury (Eid et al., 1998; Barbolina et al., 2007; Bhindi et al., 2012; Giuliani et al., 2009). In myocardial ischemia/reperfusion injury, inhibition of Egr-1 expression can lead to decrease in infarct size (Bhindi et al., 2012). It has been shown that RIPC-induced cardioprotection is associated with a decrease in Egr-1 gene expression (Konstantinov et al., 2005). Mudaliar et al. demonstrated the effect of RIPC on Egr-1 expression and showed that hypoxia-reperfusion (H/R) increases the Egr-1 transcription levels in H9c2 cells. However, RIPC attenuated the H/R induced increase in Egr-1 levels in H9c2 cells. Furthermore, it was also reported that RIPC failed to produce cardioprotection in Egr-1 overexpressed cells. The authors also delineated the linkage between RIPC, Egr-1 and free radicals. Pretreatment of H9c2 cells with polyethylene glycol-superoxide dismutase complex (PEG-SOD), a free radical scavenger, reversed RIPC-induced decrease in Egr-1 expression and resulted in increase in apoptosis of these cells. This suggests that polyethylene glycol-superoxide dismutase complex