ANTIOXIDANTS & REDOX SIGNALING
Volume 6, Number 2, 2004

Forum Editorial

Redox Control of Cardiac Preconditioning

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PRECONDITIONING is a phenomenon whereby a brief period of ischemic hypoxia renders the myocardium resistant to infarction from a subsequent ischemic insult. Preconditioning was first reported in dog heart by Murry *et al.* in 1986 (17) with brief episodes of ischemia, which caused the heart to tolerate a subsequent ischemic insult. Since then, numerous studies have been done to determine the mechanism of preconditioning. Myocardial ischemia/reperfusion injury involves damage to a variety of cell types, including myocytes, smooth muscle cells, and endothelial cells. Reperfusion of ischemic myocardium is associated with the reduction of antioxidants and generation of oxygen free radicals that play a role in the pathogenesis of ischemic reperfusion injury (5). The presence of both hydroxyl radical ($OH\cdot$) and singlet oxygen ($^1O_2$) has been documented in the ischemic reperfused myocardium (6). Thus, reactive oxygen species (ROS) (15) play a crucial role in the pathogenesis of myocardial ischemia/reperfusion injury giving rise to the "execution signal" to particular cells, which results in cell death. However, this particular ROS plays a significant role in cell signaling when needed, such as during ischemic or hypoxic preconditioning.The cardioprotective ability of ischemic preconditioning (IP) is found to be abolished when heart is preperfused with *N*-acetylcysteine, a scavenger of ROS, suggesting the role of ROS signaling or "redox signaling" in cardioprotection by IP. Evidence is rapidly accumulating to support the role of ROS as intracellular second messengers. The long-held view of oxygen free radicals being detrimental to the biological system was challenged after the recent discovery that these reactive species can function as signaling molecules (9). Biological cells, including cardiomyocytes, contain enzymes that can simultaneously generate ROS and intracellular redox buffer in response to a specific stress. Depending on the amounts of antioxidant reserve and oxygen free radicals in the system, the ROS are either destroyed or persist. Thus, the oxygen free radicals fulfill the definition of a second messenger and are either up- or down-regulated after physiological stimuli like ischemia.

The precise mechanism of IP is far from clear. It is generally believed that IP occurs in two different steps: (a) early effect (short-term adaptation) triggered over seconds to minutes, which is likely to be mediated by the release of some endogenous compound(s) such as catecholamines and adenosine, and may last up to 1–2 h (IP); and (b) late effect (long-term adaptation), which may occur after several hours and may last days to months. The long-term adaptation is believed to be mediated by the transcription of genes and their subsequent translation into proteins, and has been termed myocardial adaptation to ischemia (7). When heart is adapted to ischemic stress by repeated short-term ischemia and reperfusion, the generation of the ROS is rapidly increased, but does not increase at the same rate as in non-ischemic preconditioned myocardium during subsequent ischemia/reperfusion. The same developmental pattern of oxidative stress is observed when rats were treated with endotoxin and interleukin-1α (13, 14, 26). These interventions were found to develop oxidative stress within a very short period (4–6 h); however, they reduce subsequent oxidative stress development when hearts are subjected to ischemia/reperfusion. It has been demonstrated that cellular protein kinase C (PKC) activation is an important step in the mechanism of adaptive protection of heart (16). Several studies documented translocation of PKC by short-term ischemia, as well as ischemia followed by reperfusion (20). The results of a number of recent studies from our laboratory led us to believe that PKC may not be the ultimate link between IP and myocardial adaptation. These include the abundance of mitogen-activated protein (MAP) kinase-activated protein (MAPKAP) kinase 2 in heart, rapid activation of MAPKAP kinase 2 by stresses including heat stress, oxidative stress, and ischemia/reperfusion, and most importantly, that it is MAPKAP kinase 2, and not PKC, that can phosphorylate small heat-shock proteins, HSP25/HSP27, which are also activated by IP. Again, such adaptive response is also found to be associated with DNA binding activity of a redox sensing transcription factor nuclear factor-κB (NFκB). Increased activity of NFκB and induction of the protective proteins were blocked by pretreatment of the hearts with an oxygen free radical scavenger such as dimethylthiourea (8). However, the exact molecular link between IP and ultimate myocardial adaptation or cardioprotection is not known.

This special edition of *Antioxidants & Redox Signaling* will shed some more light on the mechanism of IP-mediated cardioprotection and will expand our knowledge on redox con-

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trol during IP. This forum issue consists of several exciting articles, including seven original articles and seven reviews.

The seven original articles are very timely and varied in their topics. Juhasz *et al.* (11) report a very interesting site of preconditioning in the diseased myocardium. Hochhauser *et al.* (10) report the role of adenosine receptors (A_1 and A_3) in the activation of antioxidative enzymes during ischemia and reperfusion. Slezak *et al.* (23) document the very interesting and important topic of nitric oxide synthase expression and its cellular control in rat cardiomyocytes. Blanc *et al.* (3) demonstrate hydrogen peroxide-induced activation of extracellular signal-regulated kinases 1 and 2, p38 MAP kinase, and protein kinase B signaling in vascular smooth muscle cells. Smiley *et al.* (24) document peroxisomal proliferation and amelioration of endocardial endothelial and muscarinic dysfunction in spontaneously hypertensive rats and the role of endothelial nitric oxide. The article by M. Nayeem (18) demonstrates the effect of sublethal simulated ischemia promotes cardioprotection by activating ATP-sensitive K^+ channels in myocytes and also discusses the possible role of PKC and inducible nitric oxide synthase. Anand-Srivastava and Fusco (1) discuss redox modulation of Gi protein expression and adenylyl cyclase signaling and the role of nitric oxide in rat myocardium.

This forum issue also consists of seven very informative and elegant review articles. Saini *et al.* (22) skillfully discuss the role of ROS at the subcellular level during IP in the myocardium. Das (4) illuminatingly explains the importance of the protein, thioredoxin, in maintaining the redox environment of the cell and its regulation of IP. Maulik (12) elegantly discusses the IP-mediated cardioprotection through the trigger of angiogenic signal, whereas Baker (2) persuasively discusses the oxidative stress-induced adaptation of the infant heart to ischemic hypoxia. Rakotovao *et al.* (21) also describe the cardioprotective role of ethanol and wine during ischemia and reperfusion. Stowe and Kevin (25) focus on the cardioprotection by volatile anesthetic agents. The last review article of this forum is by Otani (19), who documents very carefully the role of ROS as a mediator of signal transduction in IP.

The editor hopes that this forum issue will serve as an up-to-date source of information regarding the molecular mechanism of redox signaling during IP-mediated cardioprotection to scientists as well as clinicians. The editor would like to thank the contributing authors wholeheartedly for their excellent contributions and cooperation.

ABBREVIATIONS

IP, ischemic preconditioning; MAP, mitogen-activated protein; MAPKAP, MAP kinase-activated protein; NFκB, nuclear factor-κB; PKC, protein kinase C; ROS, reactive oxygen species.

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