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Mitochondria and Their Role in Ischemia/Reperfusion Injury

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14.1. Myocardial Ischemia

Acute coronary occlusion is the leading cause of morbidity and mortality in the western world and according to the World Health Organization will be the major cause of death in the world as a whole by the year 2020 (Murray and Lopez 1997). The major complication of the sudden occlusion of a coronary artery is the loss of contractile myocardium served by that artery. The contractile dysfunction resulting from infarction of the ventricle is essentially permanent as the lost heart muscle cannot regenerate. The size of the resultant infarct is the decisive determinant of the extent and severity of remodeling (Pfeffer et al. 1991) and of the prognosis of patients after myocardial infarction (St. John Sutton et al. 1997). Fast revascularization will result in less myocardial necrosis; nevertheless congestive heart failure secondary to myocardial infarction is still common.

14.2. Preconditioning the Heart

In 1986, Murry et al. first described the phenomenon of ischemic preconditioning (IPC). After dog hearts were pretreated with 4 episodes of 5 minutes of ischemia, each followed by brief reperfusion, the resulting infarct s after 40 minutes of ischemia was about one-quarter of that in animals experiencing only the 40-minute coronary occlusion. Thus, the short ischemic periods caused a rapid adaptation of hearts against infarction. This process is the most powerful protection known against myocardial infarction. Since the initial report there has been intensive research to uncover the underlying mechanisms. The protective effect of IPC is receptor-mediated. It was first discovered that activation of the adenosine A1 receptor can elicit it (Liu et al. 1991; Tsuchida et al. 1993). Subsequently other G protein-coupled receptors were found to trigger IPC like bradykinin (Wall et al. 1994; Goto et al. 1995; Cohen et al. 2001), opioid (Schultz et al. 1995; Miki et al. 1998; Cohen et al. 2001), angiotensin AT1 (Liu et al. 1995), endothelin ET1 (Wang et al. 1996), α1 adrenergic (Tsuchida et al. 1994) and acetylcholine (Thornton et al. 1993; Qin et al. 2003; Krieg et al. 2004b) receptors.
Reactive oxygen species act as second messengers in the mechanism by which bradykinin and opioid receptors trigger the preconditioned state. $G_i$-coupled receptors cause the production of ROS by a complex pathway in which phosphatidylinositol 3 (PI3)-kinase activates Akt through phosphoinositide-dependent kinases 1 and 2 which in turn activate endothelial nitric oxide synthase (NOS) (Krieg et al. 2002; Krieg et al. 2004b) (Figure 14.1).

The resulting NO stimulates guanylyl cyclase which then activates protein kinase G (PKG). PKG opens mK$_{\text{ATP}}$ by a process that involves an intramitochondrial protein kinase C (PKC) isoform (Oldenburg et al. 2004; Costa et al. 2005a). mK$_{\text{ATP}}$ channel opening then leads to the production of reactive oxygen species (ROS) by the mitochondria. Those ROS are thought to then trigger kinase cascades which ultimately lead to cardioprotection (Pain et al. 2000; Oldenburg et al. 2004; Krieg et al. 2004b). In this scheme mitochondria play an important role by being part of a signal transduction pathway and by generating ROS which serve as critical second messengers.

**Figure 14.1.** Schematic of the mechanism involved in $G_i$-coupled receptors leading to ROS generation. After ligand activation of the $G_i$-coupled receptor, the epidermal growth factor receptor (EGFR) is transactivated at its tyrosine groups through metalloproteinase (MMP)-dependent cleavage of heparin-binding EGF-like growth factor (HB-EGF) from proHB-EGF in the membrane. This in turn results in the formation of a complex with Src tyrosine kinase and phosphatidylinositol 3-kinase (PI3K) which can activate both 3' phosphoinositide-dependent kinase-1 (PDK 1) and -2 (PDK 2). This results in phosphorylation of Akt at Thr 308 and Ser 473, respectively. Akt activates endothelial nitric oxide synthase (eNOS), which in turn activates guanylyl cyclase (GC) to produce cGMP. The latter activates protein kinase G (PKG) which opens the mK$_{\text{ATP}}$ channel via PKC (not shown). Radical production by the electron transport chain is increased and these radicals are released to activate downstream kinases and protect the heart.