Cardiac Preconditioning by Anesthetic Agents: Roles of Volatile Anesthetics and Opioids in Cardioprotection

Yoshimi Inagaki

Division of Anesthesiology and Critical Care Medicine, Department of Surgery, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8504 Japan

Cardiac preconditioning is the most potent and consistently reproducible method of protecting heart tissue against myocardial ischemia-reperfusion injury. This review discussed about the signaling and amplification cascades from either ischemic preconditioning stimulus or pharmacological preconditioning stimulus, the putative end-effectors and the mechanisms involved in cellular protection. The pharmacological preconditioning induced by volatile anesthetics and opioids is very similar to the ischemic preconditioning. It includes activation of G-protein-coupled receptors, multiple protein kinases and ATP-sensitive potassium channels (K_{ATP} channels). Volatile anesthetics prime the activation of the sarcolemmal and mitochondrial K_{ATP} channels, which are the putative end-effectors of preconditioning, by stimulation of adenosine receptors and subsequent activation of protein kinase C (PKC) and by increased formation of nitric oxide and free oxygen radicals. Similarly, opioids activate δ- and κ-opioid receptors leading to activation of PKC. The open state of the mitochondrial K_{ATP} channel and sarcolemmal K_{ATP} channel ultimately induces cytoprotection by decreasing Ca^{2+} overload in the cytosol and mitochondria.

Key words: ATP-sensitive potassium channel; ischemic preconditioning; pharmacological preconditioning; volatile anesthetic; opioid

Anesthesiologists frequently meet perioperative cardiac ischemic events in the clinical anesthesia and also treat patients with ischemic heart disease. Myocardiac ischemic events lead to severe complications and delay the postoperative recovery, thereby worsening the prognosis of the patients who underwent surgery. To minimize the damage or injury of myocardium in the perioperative period is a very important factor to improve outcome of surgery. It has been known well that anesthetics have abilities to prevent ischemic myocarcial injury. Therefore, understanding the role of anesthetics including volatile anesthetics and opioids in myocardiac protection is likely to show the strategies of anesthetic management to reduce the incidence of cardiac ischemic events in the perioperative period. This short review reveals the role of volatile anesthetics and opioids in prevention myocardiac ischemic injury due to cardiac preconditioning.

Ischemic preconditioning

Ischemic precondionig is the concept introduced by Murry et al. (1986) that four cycles of 5-min

left circumflex coronary artery (Lcx) occlusion, in advance of 40-min Lcx occlusion, reduced infarct size by 75% in a canine model. Thereafter, there have been many reviews on ischemic preconditioning (Okubo et al., 1999; Nakano et al., 2000; Rubino and Yellon, 2000). Ischemic preconditioning can be observed from isolated cardiomyocytes and vascular endothelial cells to hearts in situ in various species (Okubo et al., 1999; Tomai et al., 1999a; Nakano et al., 2000; Rubino and Yellon, 2000). In humans, ischemic preconditioning enhanced postischemic contraction in ventricular trabeculae muscle and improved survival rate of isolated cardiomyocites (Tomai et al., 1999a). Moreover, in clinical application, ischemic preconditioning elicited by two periods of 3-min aortic cross clamping before cardiopulmonary bypass for valve replacement reduced myocardial enzyme leakage, free radical production and histological degeneration and increased contractility after cardiopulmonary bypass (Lu et al., 1998; Li et al., 1999). Szmagala et al. (1998) applied 4-min aortic cross clamping and 6-min reperfusion prior to coronary artery bypass grafting (CABG), thereby reducing troponin from blood samples. The present author addresses the mechanisms of ischemia-reperfusion injury before showing the possible mechanisms of ischemic preconditioning.

Ischemia precludes adequate oxygen supply, which rapidly results in depletion of ATP. This inhibits ATP-driven Na^+-K^+ pumps, increasing $[Na^+]i$. $[H^+]i$ is increased due to poor washout of metabolites and inhibition of mitochondrial oxidation of $NADH_2$. Increased $[H^+]i$ enhances Na^+-H^+ exchange to retain normal pHi, leading to increased $[Na^+]i$. Accordingly, $[Ca^{2+}]i$ is augumented via Na^+-Ca^{2+} exchange (Opie, 1998a, 1998b). High $[Ca^{2+}]i$ degrades proteins and phospholipids (Opie 1998c; Maxwell and Lip, 1997). Onset of ischemia increased the production of free radicals derived mainly from neutrophils and mitochondria (Opie 1998a; Maxwell and Lip, 1997). When coronary arteries are damaged, ischemia-related injury prevents swift gas exchange by swollen endothelial cells. Vessels with malfunctioning endothelium and smooth muscle cannot dilate when necessary. Moreover, neutrophils/platelets aggregating in the lumen decrease adequate coronary flow (Opie 1998c; Maxwell and Lip, 1997). Neutrophils release oxygen free radicals, cytokines and other proinflammatory substances, which injure the endothelium, vascular smooth muscle and myocardium (Jordan et al., 1999). A pathway for neutrophil sequestration is the specific interaction of adhesion molecules whose expression is promoted by ischemia-reperfusion. Adhesion molecules, for example, intercellular adhesion molecule-1 (ICAM-1), L-selectin and CD11b/CD18 are expressed on neutrophils and endothelium. On reperfusion, $[H^+]$ outside the cell is rapidly decreased to normal levels because of wash-out. This results in an increase in $[Ca^{2+}]i$ due enhanced Na^+-H^+ and Na^+-Ca^{2+} exchange (Opie 1998b; Opie 1998c). Reperfusion also results in a burst of free radical generation because oxygen abundantly supplied (Opie 1998c; Maxwell and Lip, 1997). Both increased $[Ca^{2+}]$ and free radicals harm the myocardium during reperfusion (Opie 1998c; Maxwell and Lip, 1997). Damage of the vascular system is more prominent during reperfusion than ischemia (Maxwell and Lip, 1997; Jordan et al., 1999). Infarction is one of the major events of ischemia-reperfusion injury during anesthesia. Another major event is myocardial stunning, which is defined as reversible myocardial dysfunction that persists after reperfusion (Opie 1998c; Bolli and Marban, 1999; Braunwald and Kloner, 1982).

Mechanisms of early preconditioning

Preconditioning is a treatment before an ischemic event while ischemia-reperfusion injury is developed during and after an ischemic period. The signals were generated by short period of ischemia in ischemic preconditioning. Ischemic preconditioning is mediated via several sacrolemmal receptors, which are mostly linked to inhibitory G (Gi)-protein (Ninomiya et al., 2002), namely
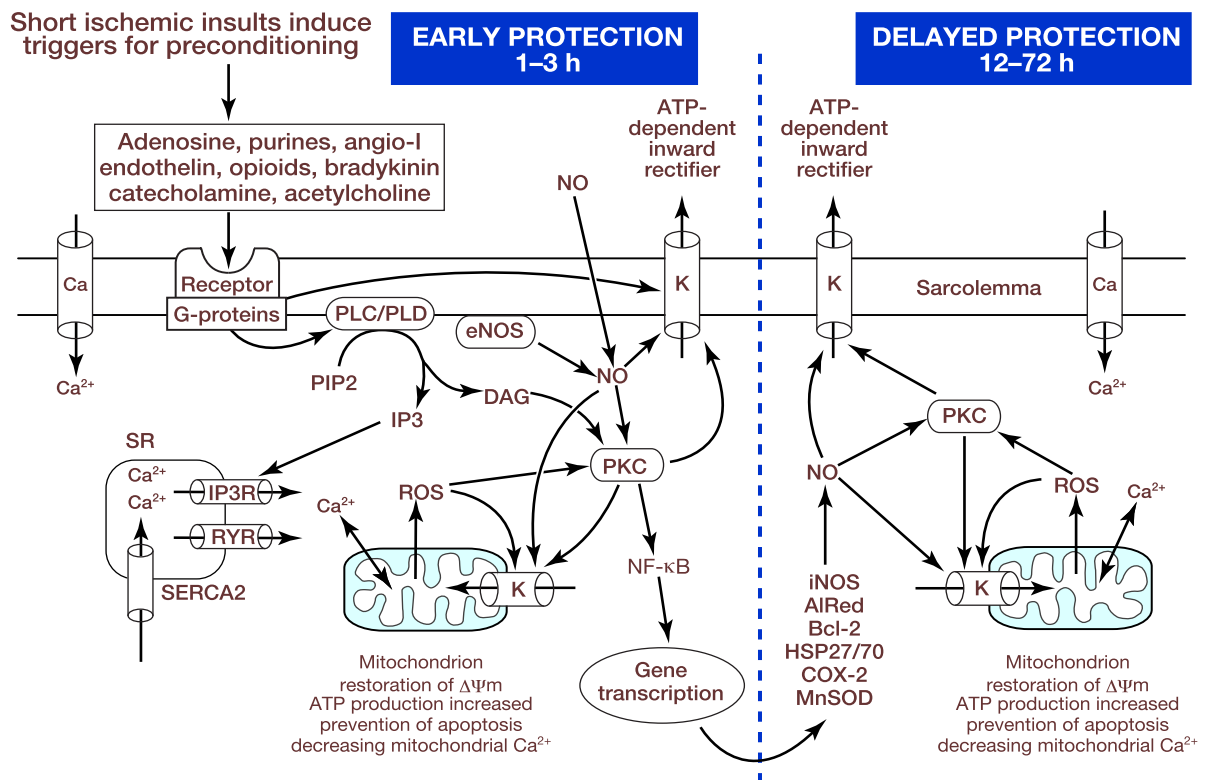
Fig. 1. Signaling for cardiac preconditioning. The left of dashed line represents mechanisms of early preconditioning and the right represents those of late (delayed) preconditioning. This figure is quoted from the reference of Zaugg et al., 2003. dym, inner mitochondrial membrane potential; AlRed, aldose reductase; Bcl-2, anti-apoptotic protein; Ca, sarcolemmal voltage-dependent Ca^{2+} channels; COX-2, cyclooxygenase type 2; DAG, diacylglycerol; eNOS, endotherial NO synthase; HSP, heat shock proteins; iNOS, inducible NO synthase; IP3, inositol triphosphate; IP3R, inositol triphosphate receptor; K, sarcolemmal and mitochondrial K_{ATP} channels; MnSOD, manganese superoxide dismutase; NF-κB, nuclear factor-κB; NO, nitric oxide; PIP2, phosphatidylinositol bisphosphate; PKC, protein kinase C; PLC/PLD, phospholipases C and D; ROS, reactive oxygen species; RYR, ryanodine Ca^{2+}-release channel; SERCA2, Ca^{2+} pump of the SR; SR, sarcoplasmic reticulum.

adenosine (A-1, A-3), purinoceptors (P2Y), endothelin (ET1), acetylcholine (M2), α_1- and β-adrenergic, angiotensin II (AT1), bradykinin (B2) and opioid (δ_1, κ) receptors, which couple to a highly complex network of kinases. The involvement of many receptors or triggers in mediating preconditioning reflects the biological redundancy in this life-saving signal transduction pathway. Figure 1 shows the main signaling steps and components of early and delayed preconditioning (Zaugg et al., 2003).

G-proteins link the initial stimulus from the individual receptors to phospholipase C and D. They have several additional functions such as inhibition of Ca^{2+} influx during ischemia, regula-

tion of cellular metabolism and activation of ATP-sensitive potassium channels (K_{ATP} channels), the putative main end-effectors of preconditioning. Activation of phospholipase C and D introduces formation of inositol triphosphate (IP3) for the release of Ca^{2+} from the sarcoplasmic reticulum via the IP3 receptor, and production of diacylglycerol (DAG). DAG activates different isoforms of protein kinase C (PKC). PKC is activated by a large number of phosphorylating enzymes, including G-proteins, phosphlipids, DAG, increased intracellular Ca^{2+}, and nitric oxide (NO), which is derived from intracellular constitutively active NO synthsae (NOS) or from extracellular sources. PKC can be activated by reactive oxygen species

(ROS) derived from mitochondria either during the short ischemic or the subsequent repetitive reperfusion episodes. Activation of this key enzyme leads to isoform-specific and cytoskeleton-mediated translocation of cytosolic PKC, inducing phosphorylation and thus activation of the sacrolemnal and mitochondrial K_{ATP} channels (Light et al., 2000). After only 10 min of ischemic preconditioning, PKC activity in the cytosol reduces, whereas PKC in the particulate fraction (i.e., nuclei, mitochondria and membranes) increases (Strasser et al., 1992). PKC-δ translocation seems to be responsible for activating mitochondrial K_{ATP} channels and PKC-ε translocation for the establishment of late preconditioning by phosphorylating nuclear targets (Kawamura et al., 1998). However, the observation that PKC inhibition may not completely block the preconditioning stimulus (Vahlhaus et al., 1996) supports the concept that additional intracellular kinases downstream, upstream or in parallel to PKC signaling contribute to the amplification and establishment of the preconditioned state. Recent studies suggested that mitochondrial K_{ATP} channels play a greater role than sacrolemmal K_{ATP} channels (Nakano et al., 2000; Rubino and Yellon, 2003).

ROS, important intracellular signaling molecules derived from mitochondria, are increased during sublethal oxidative stress (preconditioning stimulus) and play a pivotal role in triggering early and delayed cardioprotection (Cohen et al., 2001). ROS activate phospholipase C and PKC, which, in turn, amplify the preconditioning stimulus. Generation of ROS during the initiation of preconditioning represents an essential trigger for early and delayed cardioprotection. NO can induce a cardioprotective effect against myocardial stunning and infarction. Recent studies revealed direct evidence of enhanced biosynthesis of NO in the myocardium subjected to brief episodes of ischemia and reperfusion, probably via increased NOS activity (Bolli, 2001). Although NO is not necessary for ischemia-induced early preconditioning, exogenous or pharmacologically increased endogenous NO production elicits an early preconditioning effect, that is, NO is sufficient but no necessary for early preconditioning (Bolli, 2001). Conversely, NO has an obligatory role in late preconditioning (Guo et al., 1999).

Mechanisms of late preconditioning

Late preconditioning requires NO formation and increased synthesis of protective proteins (Bolli, 2001). PKC and multiple kinases are involved in the signaling cascade, leading to activation of several transcription factors, such as nuclear factor-κB (NF-κB), which leads to the sustained expression of a number of proteins considered to be responsible for the delayed protection phase. Disruption of the inducible NOS (iNOS) gene completely abolished the delayed infarct-sparing effect, which indicates the obligatory role of iNOS in the cardioprotection afforded by delayed preconditioning (Guo et al., 1999). The most likely cardioprotective effects of NO in late preconditioning are: i) inhibition of Ca^{2+} influx; ii) antagonism of β-adrenergic stimulation; iii) reduced contractility and myocardial oxygen consumption; iv) opening of K_{ATP} channels; v) antioxidant actions; and vi) activation of COX-2 with the synthesis of prostanoids. Activation of K_{ATP} channels also plays a role in delayed protection (Bernardo et al., 1999).

Sarcolemmal and mitochondrial K_{ATP} channels

Cardiomyocytes have two distinct types of K_{ATP} channels, one located in the surface membrane (sacrolemmal K_{ATP} channels) and another in the inner mitochondrial membrane (mitochondrial K_{ATP} channels). Sarcolemmal K_{ATP} channels are physically bound with the creatine phosphate-creatine kinase system and provided a direct link between metabolic state and cellular excitability. Mitochondrial K_{ATP} channels regulate mitochondrial volume state, mitochondrial membrane po-