Nitric oxide is a preconditioning mimetic and cardioprotectant and is the basis of many available infarct-sparing strategies

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Abstract

Ischemic preconditioning is a powerful infarct-sparing intervention. Intensive investigations have revealed many of the signaling steps used to elicit this protection. One of the steps involves activation of nitric oxide synthase (NOS) by phosphorylation, with the production of NO and subsequent activation of guanylyl cyclase, production of cGMP, activation of protein kinase G, opening of mitochondrial K_ATP channels, and generation of reactive oxygen species. The latter act as second messengers to activate critical kinase cascades that trigger entrance into the preconditioned state. Thus, NO exposure before ischemia can act as a powerful preconditioning mimic. Elevating NO just prior to or at reperfusion can still be an effective cardioprotective strategy. Activation of NOS or production of NO can be done pharmacologically with exogenous agents to trigger this cascade. Many of these strategies are already available and safe.

Keywords: Carbon monoxide; Cardioprotection; Natriuretic peptide; Nitric oxide; Phosphodiesterase inhibitor; Preconditioning; Statin

Ischemic preconditioning (IPC) was first introduced by Murry et al.[1] in 1986. There has not been a more potent cardioprotective intervention described before or since. In Murry’s dogs 4 brief 5-min coronary occlusions in the 40-min period preceding a continuous 40-min occlusion decreased infarct size by 75% from that seen in dogs with only the prolonged coronary occlusion. This remarkable protection has been documented in all species of experimental animals studied to date [2] as well as man [3]. Because of the impressive clinical potential of such an intervention, it has been subjected to much scrutiny during the past two decades. Because myocardial ischemia is not a clinically useful trigger of this phenomenon, the mechanism and signaling of preconditioning have been extensively studied in an attempt to identify a more appropriate and useful stimulus that could safely and reliably be applied in man to produce prophylactic protection against ischemic events. The result of these studies is that much is now known concerning IPC’s mechanism. One might ask if nitric oxide (NO) could be one of these agents.

1. History of NO in preconditioning

Although Bolli and his colleagues [4] convincingly demonstrated that endogenous NO was critical to the triggering of the second window of preconditioning (late preconditioning), its participation in the signaling of classical (early) preconditioning has until recently been quite controversial. Woolfson et al. [5] were the first to test for the involvement of NO in ischemic preconditioning. Isolated rabbit hearts were treated with $N^\text{ω}$-nitro-L-arginine methyl ester (L-NAME), a NO synthase (NOS) inhibitor, but no effect against ischemic preconditioning was seen. Interestingly, however, they noted that L-NAME reduced infarct size in non-preconditioned hearts, a phenomenon
which has not been reported since. On the other hand, Lochner et al. [6] presented evidence that NO plays a role in IPC in rat hearts. Ferdinandy et al. [7] also saw loss of protection in a pacing model of preconditioning when NOS inhibitors were administered. Regrettably our own work contributed substantially to the confusion surrounding a possible role of NO in IPC. In an early study we investigated the contribution of endogenous nitric oxide to the protection of ischemic preconditioning [8]. In an isolated rabbit heart preparation we examined the effect of L-NAME added to the perfusate. Ischemic preconditioning with 5 min of global ischemia and 10 min of reperfusion before the 30-min index ischemia resulted in dramatic salvage of myocardium (Fig. 1). When L-NAME (100 μM) was infused for 50 min beginning 5 min before the 5-min preconditioning ischemia/10-min reperfusion and ending at the end of 30 min of regional ischemia, protection was not affected. The result was the same with 200-μM L-NAME [9]. The NO donor S-nitroso-N-acetylpenicillamine (SNAP) given prior to ischemia mimicked IPC and protected the hearts [8]. We concluded that exogenously administered NO could trigger the preconditioned state but that endogenous production of NO was not involved in IPC. For several years we relied on this study to discount NO’s participation in IPC’s mechanism. However, our very recent observations have permitted us to challenge our original conclusion (see below).

2. Reactive oxygen species are involved in IPC in the in situ heart

Around that same time it was noted that reactive oxygen species (ROS) were involved in the triggering of IPC. Forbes et al. [10] reported that protection from diazoxide, a selective opener of mitochondrial ATP-sensitive potassium channels (mKATP), could be blocked with a ROS scavenger. Similarly Yao et al. [11] reported a ROS scavenger could also block protection from acetylcholine in chick myocytes exposed to simulated ischemia. That led us to formulate a hypothesis that occupancy of surface receptors during the preconditioning ischemia led to opening of mKATP channels which caused the mitochondria to release ROS. The ROS would then act as second messengers to activate protein kinase C (PKC) and its protective pathways. That hypothesis was supported by the study of Pain et al. [12]. Because it can be shown that all events leading to ROS formation must occur prior to the onset of the ischemic insult, we have termed this the trigger pathway.

3. The cardiomyocyte ROS model

To map out the signaling steps in the trigger pathway we resorted to an isolated rabbit cardiomyocyte preparation. To quantitate cell ROS production we used reduced Mitoc...
Tracker red, a non-fluorescent probe, which, when oxidized by ROS, becomes fluorescent and binds to thiol groups in mitochondria. When cardiomyocytes were exposed to ACh, bradykinin, or opioids, the G protein-coupled receptor (GPCR) agonists known to trigger preconditioning, ROS production was increased. We were able to show that in general these agents act to cause a metalloproteinase-dependent activation of the epidermal growth factor (EGF) receptor which, through a Src-kinase-dependent mechanism, activated phosphatidylinositol 3-kinase (PI3-K) and Akt (Fig. 2). Thus the increased ROS production induced by these agents could be blocked by inhibiting metalloproteinase [13], blocking the EGF receptor [13], inhibiting Src kinase [14], inhibiting PI3-K [14,15] and Akt [16], or closing mKATP channels [14,17], respectively. But then we noted that L-NAME would also block ROS production [16,17], implying NOS was indeed part of the trigger pathway. Given our earlier results in the isolated heart, these data in cardiomyocytes were confusing.

4. The trigger pathway

As a result of these investigations many of the signaling steps of IPC’s trigger pathway have now been elucidated. As depicted in Fig. 2 we now believe that during preconditioning the ischemic myocardial cell releases at least 3 receptor agonists that bind to G_i or G_q protein-coupled receptors. They include bradykinin, opioids, and adenosine. These agonists then initiate a complex signaling cascade which ultimately leads to protection. To facilitate the early investigations most of these steps were first established with acetylcholine (ACh), an agonist of a well characterized GPCR although ACh is not released by ischemic myocardial cells. However, ACh’s signaling exactly mimics that of opioids and, with a small exception, bradykinin. Curiously adenosine bypasses many of these early trigger steps and appears to activate a downstream kinase cascade directly.

We believe that the trigger pathway proceeds as follows. There is considerable evidence that these agonists first cause transactivation of the EGF receptor [13,18,19]. After the released agonists bind to their respective receptors, the G protein’s βγ subunits are liberated and shuttle within the sarcolemma where, among other things, they activate a membrane metalloproteinase. The metalloproteinase cleaves heparin-binding EGF-like growth factor (HB-EGF) from its inactive pro-form. HB-EGF then binds to the EGF receptor which dimerizes leading to auto-phosphorylation of critical tyrosine residues (termed transactivation) resulting in attraction of several proteins including Src tyrosine kinase and PI3-K which assemble into a signaling complex. PI3-K is activated and it phosphorylates membrane phosphatidylinositol bisphosphate in the 3 position. The 3-phosphorylated phospholipid then activates the phosphoinositide-dependent kinases (PDKs) which in turn activate Akt through phosphorylation [20].

Akt (or protein kinase B) in turn phosphorylates endothelial NOS (eNOS) [21] which catalyzes formation
of the powerful small molecular messenger NO. NO stimulates soluble guanylyl cyclase to increase production of cGMP which in turn activates protein kinase G (PKG). Cytosolic PKG then phosphorylates some unknown target on the mitochondria’s outer membrane which then through a PKC isoform in the mitochondria (likely ε) causes the ATP-sensitive K+ channel on the inner membrane to open [22]. As a result K+ enters the mitochondrion along its electrochemical gradient resulting in alkalization of the matrix [23] and increased production of ROS. Although initially regarded to be deleterious elements promoting DNA and protein oxidation, membrane disruption, and organelle destruction, ROS are critical elements in this signaling pathway. Thus interference with ROS production after triggering of preconditioning with ischemia can abort cardioprotection while controlled production of ROS in lieu of another preconditioning stimulus can decrease infarction [24,25]. When released from mitochondria ROS act as second messengers and are thought to activate phospholipase C and PKC. That initiates the mediator pathway which leads to activation of PI3 kinase and extracellular signal-regulated kinase (ERK) at reperfusion [26,27] and inhibition of mitochondrial permeability transition pore formation [28]. The pore is thought to be the end-effector. The signaling within the mediator pathway is less well understood than that of the trigger pathway. However, it is now thought that the actual protection occurs in the reperfusion rather than ischemic phase, and repopulation of adenosine receptors [27] and activation of multiple kinases [26,27] are critical events.

5. Adenosine uses a pathway independent of NO

While both opioids and bradykinin trigger IPC through the NO-dependent pathway described above, adenosine uses an entirely different pathway. Adenosine-triggered protection cannot be blocked by KATP channel blockers [29], ROS scavengers [29], or NO blockers [30]. Adenosine appears to trigger IPC by coupling directly to PKC. Although this observation was surprising since adenosine presumably couples to the same G protein as bradykinin and opioids, the different pathway followed by adenosine appears to afford the organism increased security. The redundancy insures the continuing ability to precondition the heart even if there is blockade or interference with the trigger pathway at one of the intermediate steps as EGFR, Akt or NO. It is presumed that once PKC is activated by adenosine or some other preconditioning trigger, the mediator pathway is the same independent of the specific trigger.

6. NO does participate in IPC in the in situ heart

Obviously the cell data did not agree with our [8] or Woolfson’s [5] previous observation that IPC’s protection in an isolated heart could not be blocked by L-NAME. We now believe that those observations were the result of use of the isolated heart model. The 3 major agonists released by the ischemic heart are bradykinin, opioids, and adenosine. In the isolated buffer-perfused heart the absence of circulating kininogens would minimize any release of bradykinin. And the absence of cardiac innervation would attenuate opioid release. Thus virtually all of the triggering would come from adenosine which, unfortunately, bypasses the NO-dependent trigger pathway. Therefore, it would not be surprising that NO is unimportant in the isolated heart. We hypothesized that in the in situ heart where bradykinin and opioids would be released by ischemic myocardium the NOS-cGMP-PKG cascade would be important. Accordingly, we recently repeated our L-NAME experiments in the in vivo heart. IPC with 1 cycle of 5-min ischemia/10-min reperfusion decreased infarction from 38.5 ± 3.4% in control hearts to 14.7 ± 3.3% (p < 0.001). L-NAME blocked the protection of ischemic preconditioning (Fig. 1). When the number of preconditioning cycles was increased to 3, L-NAME could no longer block the protection. Presumably the additional preconditioning cycles increased the amount of released adenosine so that it alone was sufficient to protect even though the NO-dependent pathways had been blocked. Although our initial observation in isolated hearts was accurate, we mistakenly extrapolated the conclusion to all models. Hopefully these new data will set the record straight.

7. NO is a cardioprotectant

There has been an ongoing debate as to whether NO is a protectant or a source of injury in the ischemic heart. NO can be a source of deleterious peroxynitrite in the heart. Woolfson et al. [5] proposed that L-NAME protected by preventing peroxynitrite formation. However, most others see NO as a protectant. Nossuli et al. [31] documented infarct-sparing properties of exogenous peroxynitrite. Several reports have documented the deleterious effect of NOS blockers in ischemia-reperfusion injury. Williams et al. [32] and Hoshida et al. [33] observed that either L-NAME or L-nitro arginine, both NOS inhibitors, given prior to coronary occlusion in in situ rabbit preparations resulted in significantly larger infarcts than in untreated animals. And L-NAME can exacerbate post-ischemic contractile function in isolated rat hearts [34]. The strongest evidence that NOS and NO play important roles in cardioprotection is derived from experiments in genetically altered mice. Brunner et al. [35] created transgenic mice overexpressing human eNOS exclusively in cardiac myocytes. Left ventricular pressure was reduced by a maximum of 33% and basal cardiac cGMP was increased twofold, changes which were reversed by NOS blockade with L-NAME. Relative to baseline, recovery of left ventricular developed pressure and dP/dt following ischemia were significantly better in transgenic hearts (95–98%) than wild type hearts (48–51%). Again L-
NAME abolished the difference. Jones et al. [36] studied strains of mice overexpressing either bovine or human eNOS. In an in vivo preparation a coronary artery was occluded for 30 min and infarct size was determined by triphenyltetrazolium chloride (TTC) staining after 24 h of reperfusion. Myocardial infarct size was reduced by 32–33% in the two transgenic strains (p < 0.05 vs. non-transgenic mice).

Parallel experiments have been performed in eNOS knockout mice. Kanno et al. [37] studied a strain developed at the University of North Carolina (UNC). Isolated hearts with this genetic defect subjected to 30 min of global ischemia and 60 min of reperfusion had smaller, not larger, infarcts than wild type murine hearts (20.0% vs. 30.2% of risk zone, p < 0.05). This seemingly anomalous result was further investigated. Despite the missing enzyme the eNOS knockout hearts released significant amounts of nitrite into the effluent during reperfusion, implying significant production of NO. And immunobLOTS showed that iNOS was markedly induced in the eNOS knockout hearts. It was the compensatory increase in iNOS that salvaged these hearts. This conclusion was further supported when Sharp et al. [38] evaluated responses of this UNC eNOS knockout strain of mouse as well as a second Harvard knockout strain in which there was no compensatory increase in iNOS. Whereas UNC mice exhibited a 52% reduction in myocardial infarction compared to wild type controls (p < 0.05), the Harvard mice experienced an 84% increase in myocardial necrosis (p < 0.05). Furthermore an iNOS inhibitor exacerbated the extent of myocardial damage in UNC mice, but had little effect in the Harvard mice. These data certainly support the contention that NOS and NO are critical components of the cardioprotective mechanism.

8. NO-promoting strategies protect both prior to ischemia and at reperfusion

In light of this recognition many attempts to stimulate NO production with exogenous pharmacologic agents have been made. Even before the above evidence supporting the importance of NO was available, investigators were administering L-arginine, the required precursor for production of NO, just before and/or during reperfusion and observing smaller infarcts and improved recovery of post-ischemic left ventricular function in dogs [39], cats [40], and rats [34]. A variety of compounds known as NO donors are metabolized in vivo to release NO. Many investigators have examined the effect of SNAP. Kanno et al. [37] demonstrated that SNAP raised nitrite levels strikingly in the coronary effluent from buffer-perfused, isolated wild type mouse hearts. In hearts undergoing 30 min of global ischemia and 60 min of reperfusion SNAP infused into the aortic cannula’s side branch immediately after clamping of the cannula decreased average infarct size from 30.2% in untreated hearts to 16.5%. We [8,9] have observed similar effects in isolated rabbit hearts in which SNAP infused prior to the index ischemia decreased infarction from 30.2±3.3% of the risk zone in control hearts to 4.4±1.9%. Other NO donors [34,41–44], including sodium nitroprusside [45] and nitroglycerin [46,47], infused either before hypoxia or ischemia or just before reperfusion similarly salvaged ischemic myocardium and improved post-ischemic contractile function. Conversely L-NAME caused further deterioration. Nitroglycerin can also trigger delayed preconditioning (discussed elsewhere in this focused issue) [47].

A new group of NO donors in which the NO moiety is attached to an aspirin backbone were synthesized to protect the gastric mucosa against the deleterious effect of aspirin. NCX 4016 (2-acetoxybenzoate 2-[1-nitroxy-methyl]-phenyl ester) has multiple biologic actions including antithrombotic and platelet antiaggregatory effects and diminution of adherence of neutrophils to vascular endothelium. NCX 4016 resulted in rapid release of NO in rats [48] and man [49]. It also increased in a dose-dependent manner plasma cGMP levels and attenuated infarction in rats when administered orally for 5 days before 30 min of coronary artery occlusion [50]. NCX 4016 also diminished infarction in pig hearts in contrast to aspirin, although both drugs had similar inhibitory effects on platelet aggregation and thromboxane generation [51]. Interestingly in the latter model NCX 4016 had no effect on leukocyte adhesion to normal coronary arteries or those previously exposed to ischemia/reperfusion. This drug has been introduced for small clinical trials [52], but it has not yet been examined for an effect on ischemic myocardium.

Other strategies have also been used to increase circulating NO levels. Nitrite is typically thought of as the major oxidative metabolite of NO, an inert metabolic end-product with limited intrinsic biological activity. However, at low tissue pH and oxygen tension, conditions favored in ischemic myocardium, nitrite may be reduced to NO by disproportionation (acidic reduction) or by the enzymatic action of xanthine oxidoreductase. Solutions of sodium nitrite were infused 5 min before reperfusion into the left ventricular cavity of in situ mice in which coronary occlusion was maintained for 30 min followed by reperfusion for 24 h [53]. Infarct size was measured after staining with TTC. Consistent with hypoxia-dependent nitrite bioactivation, nitrite was reduced to NO, S-nitrosothiols, N-nitrosamines, and iron-nitrosylated heme proteins within 1 min of reperfusion. Nitrite administration decreased myocardial infarction by 67% compared with nitrate-treated controls. This protective effect was abolished in animals pretreated with the NO scavenger 2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (PTIO).

9. PDE-5 inhibitors

Kukreja and colleagues [54–56] have championed the cardioprotective properties of sildenafil (Viagra), probably
the most widely used drug for treatment of erectile dysfunction. It is a selective inhibitor of phosphodiesterase-5 (PDE-5) that catalyzes the breakdown of cGMP. Therefore, sildenafil enhances NO-driven cGMP accumulation. When given to rabbits either intravenously or orally it has a preconditioning-mimetic effect. Infarction averaged $33.8 \pm 1.7\%$ in untreated hearts, whereas infarct size was significantly lower ($10.8 \pm 0.9\%$) after 30 min of sildenafil pre-treatment [54]. Similar results have been observed in rats [57]. Following sildenafil injection in mice eNOS mRNA increases with a peak at 45 min and inducible NOS (iNOS) mRNA peaks at 2 h [55]. Coronary occlusion 24 h later was accompanied by a 75% decrease in infarction, and this salutary effect was blocked by an iNOS inhibitor. A very recent investigation in isolated adult mouse ventricular myocytes subjected to simulated ischemia and reoxygenation demonstrated that sildenafil pre-treatment decreased cell necrosis and apoptosis [56]. Sildenafil-induced protection against both necrosis and apoptosis was absent in myocytes derived from iNOS knockout mice and attenuated in eNOS knockout myocytes. Therefore sildenafil produces a direct protective effect through the NO signaling pathway independent of hemodynamic alterations. Although sildenafil itself does not increase NO generation, it enhances sensitivity to NO by its effective inhibition of cGMP degradation and thus augments PKG activation and the following dependent events which lead to cardioprotection. Sildenafil is currently used clinically for treatment of penile erectile dysfunction and pulmonary hypertension. It has not yet been evaluated in the treatment of ischemic heart disease, and this may be a problem because of the induced hypotension caused by concomitant use of this drug and nitrates.

10. HMG-CoA reductase inhibitors

Statins, inhibitors of HMG-CoA reductase, were introduced to lower serum cholesterol. However, their many pleiotropic actions have been utilized to affect many biological processes, and may even be more important than their effects on lipids [58]. Statins upregulate NOS activity predominantly by posttranscriptional mechanisms [59,60] and increase NO production under baseline conditions and after hypoxia [61]. Statins increase eNOS expression by increasing eNOS mRNA stability [59]. Additionally statins activate Akt, resulting in phosphorylation of eNOS and further increases in NO production [62]. Aortic rings from rats treated 18 h before sacrifice with simvastatin released twice as much NO as aortic rings from untreated animals [63]. L-NAME inhibited the NO release.

Statins have been shown to be cardioprotective in a variety of animal models. In isolated rat hearts perfused with polymorphonuclear leukocytes subjected to 20 min of global ischemia and 45 min of reperfusion, post-ischemic left ventricular function was significantly better in hearts pretreated with simvastatin [63]. In situ mice undergoing 30 min of coronary occlusion and 24 h of reperfusion, pretreatment with simvastatin significantly reduced infarction by more than 50% ($p<0.01$) [64]. This salvage by simvastatin was completely lost if the Harvard strain of eNOS knockout mice was substituted for wild type animals. Fluvastatin 20 min prior to left coronary artery ligation in rats was sufficient to preserve myocardial blood flow and decrease infarct size following 50 min of ischemia and 60 min of reperfusion [65]. L-NAME abolished fluvastatin’s effect on infarction. Postulated mechanisms of this statin infarct-sparing effect include decreased polymorphonuclear leukocyte infiltration, decreased leukocyte rolling, and decreased expression of adhesion molecules [58]. Statins have been used clinically for many years for the treatment of hypercholesterolemia, and are currently being administered very early in the treatment of patients with acute coronary syndrome [66]. However, the effectiveness of these drugs as adjuncts to percutaneous coronary intervention has not yet been examined.

11. Natriuretic peptides

Natriuretic peptides (NP) are endogenous hormones released by distended atria and ventricles. Both atrial NP (ANP) and brain NP (BNP) bind to membrane NP receptors which are expressed on cardiomyocytes. Receptor binding results in activation of particulate guanylyl cyclase, distinct from the soluble guanylyl cyclase in the NO-cGMP-PKG signaling cascade. Both BNP administered before the index ischemia in rats [67] and ANP infused a few minutes before reperfusion in rabbits [68] decreased infarct size. Examination of signaling in isolated rabbit cardiomyocytes confirms that ANP binds to a membrane NP receptor/particulate guanylyl cyclase which results in activation of PKG (unpublished observation). Unexpectedly, however, 1H-[1, 2, 4]oxadiazolo-[4, 3-a]quinoxalin-1-one (ODQ), a putative soluble guanylyl cyclase inhibitor, blocked ANP’s signaling and the natriuretic peptide’s infarct-sparing quality [68]. Although not widely appreciated there is experimental evidence that ANP stimulates eNOS and NO production [69–72]. So it appears that, at least in part, the cardioprotection triggered by natriuretic peptides involves increased production of NO. A clinical trial of the use of ANP as an adjunct to percutaneous coronary intervention in the treatment of acute myocardial infarction is ongoing [73].

12. Carbon monoxide

Carbon monoxide is produced by the endogenous degradation of heme by several heme oxygenase enzymes: the constitutively expressed HO-2 and the inducible HO-1. Like NO, CO is a versatile signaling molecule and, also like NO, it possesses vasorelaxing properties. Certain
transition metal carbonyls liberate CO under appropriate conditions and function as CO-releasing molecules (CORM). Effects of the water-soluble tricarbonylchloro-(glycinate) ruthenium II (CORM-3) have been examined in isolated, buffer-perfused rat hearts undergoing global ischemia for 30 min and reperfusion for 60 min [74] and in in situ mouse hearts subjected to 30 min of coronary occlusion and 24 h of reperfusion [75]. CORM-3 was administered either in the last minutes of ischemia and/or the early minutes of reperfusion. This CO-releasing compound diminished infarction in these models by 50–75%. Although the mechanism of this salutary effect has not been fully elucidated, closing of mitochondrial K_{ATP} channels aborts the infarct-sparing property of CO [74]. Inhaled CO in rats also diminished infarction following a 30-min occlusion of the left anterior descending coronary artery and activated Akt, eNOS and cGMP in myocardium [76]. Wortmannin, a PI3-K inhibitor, L-NAME, and methylene blue, a soluble cGMP inhibitor, each attenuated the protection by CO. This protective effect, therefore, was at least in part dependent on activation of the NOS signaling cascade. Interestingly NO may in part protect ischemic myocardium by triggering CO signaling generated by the activation of heme oxygenase [77].

13. NO: a potential role in cardioprotection

As detailed in the foregoing discussion NO supplied in multiple forms can salvage ischemic myocardium and diminish infarction. NO applied prior to ischemia clearly acts as a signal in a cascade that triggers entrance into the preconditioned state. Much more elusive is its specific role when administered at reperfusion. Augmenting NO at reperfusion appears to be associated with protection but its mechanism at that time remains speculative. It is acknowledged that NO has multiple biologic actions, including effects on inflammation, endothelial expression of adhesion molecules, and anti-platelet and antithrombotic properties. These latter effects may certainly enhance any cardioprotective quality of NO [34]. However, documentation of NO’s infarct-sparing ability in cell-free, isolated, buffer-perfused hearts diminishes the importance of the above attributes, and the isolated cardiomyocyte studies further support a role of NO on cardiomyocytes in the absence of endothelial cells.

It is important to differentiate between strategies in which pharmacologic agents are administered before the index ischemia as opposed to those in which they are administered at the time of reperfusion. In a patient presenting to the emergency room after the onset of myocardial infarction, pre-ischemic therapy can no longer be initiated. In this case reliance must be placed on those strategies found to be effective when applied after the onset of ischemia. Agents like nitrates, nitrates, ANP and CORM have shown such efficacy in animal models, but unfortunately lack confirmation in clinical trials. Finally, most patients with acute myocardial infarction already receive nitrate therapy and it is possible that they may already be maximally protected.

Preconditioning with a treatment before ischemia could also have a clinical role. In iatrogenic ischemia as occurs with cardiac surgery the patient can be preconditioned, although other cardioprotective strategies such as cooling and cardioplegia have been the treatments of choice. Since it can never be predicted when a coronary thrombus might occur, it would be impossible to time the administration of a single dose of a preconditioning mimetic to have a clinically significant effect. But chronic treatment would be expected to have a prophylactic protective effect either by continuing stimulation of the pathway outlined in Fig. 2 or triggering delayed preconditioning or the second window of protection (described elsewhere in this focused issue). That of course requires that tachyphylaxis [78] be avoided. Statin and nitrate therapies would be expected to be candidates for this strategy. We have reviewed several papers above which indicate that NO can trigger the second window type of protection.

14. Conclusion

Cardioprotection either as a prophylactic measure or as a therapeutic intervention during myocardial infarction is as yet an unrealized dream. Although the concept is attractive, admittedly not all questions have been answered by the ongoing intensive investigation. Nonetheless there are sufficient safe and seemingly effective approaches that can be used even now. A coalition between the medical community and the pharmaceutical industry is necessary to have this concept emerge from the research laboratory into the clinical arena.

References


