Prologue: nonclassical modalities of myocardial preconditioning

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CLASSICAL ISCHEMIC PRECONDITIONING (IPC) occurs when single or multiple brief periods of coronary artery occlusion interspersed with brief periods of reperfusion precede a prolonged ischemic insult (3). IPC has been shown to result in a marked reduction of myocardial infarct size in all species studied and has been shown by some investigators to reduce myocardial stunning or the incidence of cardiac arrhythmias, although evidence for these latter effects is not as convincing (5). IPC possesses two windows of cardioprotection, an early phase in which the protection only lasts for 1–2 h and a delayed phase during which the protection recovers at 18–24 h following the original IPC stimulus. The second window of IPC may persist for as long as 24–72 h (2). Numerous investigators (4) have published a plethora of papers concerning the ligands, receptors, and intracellular signaling pathways that are responsible for producing this remarkably efficacious cardioprotective effect. A consensus is growing suggesting that several diverse G protein-coupled receptors are triggers of classical early and late IPC and that stimulation of these receptors results in a cardioprotective signaling cascade, which includes (but is not necessarily limited to) reactive oxygen species (ROS), nitric oxide (NO), protein kinase C (PKC), protein tyrosine kinases (PTKs), mitogen-activated protein kinases (MAPK), and the ATP-regulated potassium (KATP) channel. Whether an effector or mediator (or both), the KATP channel in mitochondria is central to the process of IPC. In this and the next issue of the AJP: Heart and Circulatory Physiology, the Special Topic, “Nonclassical Modalities of Myocardial Preconditioning,” is showcased. Several new approaches for producing or mimicking the phenomenon of IPC via enhancing endogenous mechanisms already present in the heart or via previously unrecognized signaling pathways or pharmacological agents will be described.

On the basis of work performed using ischemia as the preconditioning stimulus, a number of approaches have been developed that mimic IPC. Some of the more important pharmacological agents that have been studied include adenosine and its agonists, bradykinin, opioids, and catecholamines (1). In the issue, the highlighted papers suggest that there may be nonclassical approaches that can be used to mimic both early and late IPC. These include evidence of several novel pathways that may also participate in the ability of myocardium to adapt to an injurious insult (sphin-gosine-1-phosphate and ganglioside GM-1 pathway) and methods for enhancing cardioprotective mechanisms that are already endogenously present in the myocardium (hypothermia, heat shock proteins, protease receptor-2 activation, food restriction, and resveratrol, a substance found in grapes and wine). Multiple papers also present strong evidence to support the concept of preconditioning from a distance by exposing another organ to an ischemic insult and observing a subsequent protective effect in the heart (mesenteric and renal IPC). IPC of the myocardium may also offer protection of other tissues. Mechanisms by which intraorgan preconditioning produces cardioprotective effects (adenosine, opioids) are addressed. Several papers focus on the role of different anesthetics to mimic (isoflurane) or, alternatively, to block IPC (ketamine). The importance of a known risk factor for cardiovascular disease, diabetes, on isoflurane-induced preconditioning is discussed. Finally, several papers address the phenomenon of delayed preconditioning. The role of reperfusion time in determining the efficacy of adenosine in producing its delayed cardioprotective effect and the central role that nitric oxide synthase plays as a trigger and mediator of late PC produced by systemic hypoxia are detailed.

These articles suggest that the powerful cardioprotective effect produced by IPC continues to fascinate researchers searching for the “magic bullet” for patients at risk of ischemic heart disease and myocardial...
infarction. These studies also describe innovative new ways in which the heart can be preconditioned in the presence of lesser degrees of ischemia or in the total absence of ischemia and methods for enhancing endogenous cardioadaptive mechanisms for therapeutic benefit.

REFERENCES


