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Nrf2-dependent upregulation of antioxidative enzymes: a novel pathway for hypoxic preconditioning-mediated delayed cardioprotection

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Abstract It has been well demonstrated that hypoxic preconditioning (HPC) can attenuate hypoxia/reoxygenation (H/R)-induced oxidant stress and elicit delayed cardioprotection by upregulating the expression of multiple antioxidative enzymes such as heme oxygenase-1 (HO-1), manganese superoxide dismutase (MnSOD) and so on. However, the underlying mechanisms of HPC-induced upregulation of antioxidative enzymes are not fully understood. Nuclear factor erythroid 2-related factor 2 (Nrf2) is an essential transcription factor that regulates expression of several antioxidant genes via binding to the antioxidant response element (ARE) and plays a crucial role in cellular defence against oxidative stress. Here, we wondered whether activation of the Nrf2–ARE pathway is responsible for the induction of antioxidative enzymes by HPC and contributes to the delayed cardioprotection of HPC. Cellular model of HPC from rat heart-derived H9c2 cells was induced 24 h prior to H/R. The results showed that HPC efficiently attenuated H/R-induced viability loss and lactate dehydrogenase leakage. In addition, HPC increased nuclear translocation and ARE binding of Nrf2 during the late phase, upregulated the expression of antioxidative enzymes (HO-1 and MnSOD), inhibited H/R-induced oxidant stress. However, when Nrf2 was specifically knocked down by siRNA, the induction of antioxidative enzymes by HPC was completely abolished and, as a result, the inhibitory effect of HPC on H/R-induced oxidant stress was reversed, and the delayed cardioprotection induced by HPC was also abolished. These results suggest that HPC upregulates antioxidative enzymes through activating the Nrf2–ARE pathway and confers delayed cardioprotection against H/R-induced oxidative stress.

Keywords Hypoxic preconditioning · Nrf2–ARE pathway · Hypoxia/reoxygenation · Oxidative stress · Delayed cardioprotection

Introduction

Ischemic preconditioning (IPC) was originally recognized by Murry et al. [1] and defined as an endogenous adaptive response to brief periods of ischemic stress that protects the myocardium against the severe consequences of a subsequent and more prolonged ischemic insult. The profound protective phenomenon also occurs in vitro in cultured cardiomyocytes followed with hypoxic preconditioning (HPC) [2–4]. Considerable evidence shows that not only IPC, but HPC also can confer two distinct phases of cardioprotection: an acute (or early) protective phase with immediate onset lasting over the course of 3–4 h and a delayed (or late) protective phase manifesting approximately 12 h after the preconditioning stimulus that can last up to 72 h [5, 6]. At present, the delayed cardioprotection has been focused with considerable interests in a clinical point of view because of its sustained duration and effective protection against both myocardial infarction and stunning [7], and its underlying mechanisms have therefore been the subject of extensive research.

It is now well established that the delayed protective mechanisms of preconditioning involve upregulation of the

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