Spotlight on cardioprotection against ischemia-reperfusion injury

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Worldwide, coronary heart disease (CHD) causes approximately one-third of all deaths in men and one-quarter of all deaths in women and represents a significant threat to public health. The global burden of CHD in terms of disability-adjusted life years (DALY) or “healthy years of life lost” is projected to increase from around 47 million DALY globally in 1990 to 82 million in 2020[1].

Myocardial ischemia-reperfusion (I/R) injury is a manifestation of CHD in patients undergoing thrombolysis or percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI), patients undergoing cardiac bypass surgery, or patients surviving cardiac arrest. Novel cardioprotective strategies aimed at improving the clinical outcomes of patients with CHD by triggering intrinsic adaptive responses to protect the heart against I/R injury are increasingly needed.

Prior to 1986, the concept of cardioprotection in the setting of AMI was purely theoretical. In 1986, the team of Murry et al.[2] reported a most unusual observation: several cycles of brief I/R occurred before a long coronary occlusion, named ischemic preconditioning (IPC), resulted in reduced size of myocardial infarct in canine hearts. Then Downey’s laboratory made the first conceptual breakthrough in how IPC protects the heart: a brief infusion of an adenosine analogue in lieu of brief ischemia protected the heart, but treatment with an adenosine receptor antagonist abolished the protection of IPC[3].

Since then, much progress has been made in understanding the signal transduction pathways in various models and forms of cardiac protection. Of particular interest is the recent development of potential strategies for protecting the heart by ischemic postconditioning (I-Post)[4], pharmacological preconditioning (PPC)[5,6], remote preconditioning (RPC)[7], or intermittent hypoxic adaptation (IHA)[8,9]. This Special Issue has highlighted research progress into novel approaches, signaling pathways and cross-talk, herbal medicine, and mitochondrial mechanisms, as well as study strategies in this exciting field of cardioprotection.

The IPC phenomenon, as one intervention for protecting the ischemic heart, has been confirmed in all species examined. IPC has also been applied clinically, for patients undergoing cardiac bypass surgery or those with unstable angina. However, IPC would be impossible to implement in patients with an unpredicted onset of myocardial ischemia. Alternatively, I-Post, reported 4 years ago by Vinten-Johansen’s group[4], offers an interventional strategy that can be applied at the time of myocardial reperfusion, a target of interest for cardioprotection[10], for AMI treated with PCI[1]. However, the application of IPC or I-Post is limited by their invasive nature. In this regard, cardioprotection induced by RPC and IHA has their merits.

Interestingly, emerging evidence suggests that different cardioprotective approaches appear to recruit similar protective pathways. During the ischemic phase, cardioprotection involves transactivation of growth factor receptors, activation of membrane enzymes and metabolism of lipids, activation of the Akt pathway, stimulation of nitric oxide production and subsequent activation of protein kinase G and C, opening of mitochondrial ATP-dependent K+ channels, inhibition of mitochondrial and cytosolic Ca2+ overloading, and release of reactive oxygen species. During the reperfusion phase, cardioprotection involves cell-surface receptors and a diverse array of protein kinase cascades, including the reperfusion injury survival protein kinase pathways such as protein kinase G, C, and A, the MAPK family, the PI3K-Akt cascades, the JAK-STAT pathway, and redox signaling. All of the signaling is now believed to lead to prevent formation of the mitochondrial permeability transition pore, which normally kills mitochondria in the first minutes of reperfusion in the unprotected heart. A better understanding of the different elements within the signal transduction cascades and their hierarchic order is of utmost importance to potentially utilize cardioprotective approaches in the clinical setting and in drug development.

In closing, although this Special Issue reflects only part of research progress in this area, we hope the Issue can provide a platform for investigators in this area to exchange their thoughts and promote the interests and collaboration of cardiovascular researchers. We would like to thank all the authors for their contributions with their novel findings and their
insights into the current state of the art in cardioprotection. We also thank Mr. WEI Bin and his staff at the editorial office of APS for their hard work to make this Special Issue possible. Finally, we thank Professor ZHU Pei-Hong, and YAO Tai, the Editor-in-Chief of APS, for giving us the opportunity to edit this Special Issue, a part of the celebration of the 80th anniversary of the founding of Acta Physiologica Sinica (continuing The Chinese Journal of Physiology). Taking this opportunity, we give our best wishes for the further development of APS in “facing the world” and hope to see more contributions devoted to Cardioprotective Research.

REFERENCES

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Dr. YANG Huang-Tian received her B.S. in Medicine in 1982 from Nantong University School of Medicine and M.S. in Medicine in 1988 from Suzhou University School of Medicine. Then she received her Ph.D. from Yamagata University School of Medicine, Japan in 1994, and served as a faculty member in the Department of Pharmacology there up to 1997. In the same year, she moved to NIH/NIA to continue her research on cardiac receptors and signaling regulation and took current position since 2000.

Dr. YANG is members of the Standing Committees of Chinese Association for Physiological Sciences, Chinese Association of Pathophysiology in Cardiovascular Sciences and in Receptors and Signal Transduction, the International Society for Heart Research-China Section, and Chinese Society of High Altitude Medicine, a member of Chinese Society for Cell Biology and Vice-Director of Shanghai Society for Physiological Sciences. She serves as a Standing Editor on the Editorial Board of *Acta Physiologica Sinica*.

The long-term goal of Dr. YANG’s laboratory is to elucidate the regulatory mechanisms underlying the physiological and pathological alterations in cardiac contractile function, and to identify novel targets and therapeutic intervention for the prevention and treatment of ischemic injury and heart failure. The laboratory is currently conducting the researches in the following aspects: (1) regulation of Ca²⁺ signaling in cardiomyocytes under development and ischemic injury; (2) differentiation of embryonic stem cells to cardiomyocytes and the therapeutic potential in ischemic heart diseases and heart failure; (3) signal transduction pathways mediated by G protein-coupled receptors and their roles in the regulation of myocardial contractility and cardioprotection; and (4) molecular and cellular basis of hypoxic adaptation- and natural compounds-induced cardioprotection against ischemic injury.

Dr. YANG and her team have identified cardioprotective roles of intermittent hypoxia and subtype of α1-adrenoreceptors against I/R-induced Ca²⁺ overload injury and the mechanisms underlying prevention of I/R-induced Ca²⁺ overload (*Am J Physiol Heart Circ Physiol* 2005; 288: H2594-H2602; *Am J Physiol Cell Physiol* 2006; 290: C1221-C1229; *Cardiovasc Res* 2007; 75: 584-595). They also demonstrated a novel repressive role of E2F6 in stress-induced apoptosis and its regulatory mechanisms (*Cell Death Differ* 2007; 14: 807-817). To address a therapeutic prerequisite of embryonic stem (ES) cells, she and her colleagues have revealed the functional properties of potential replacement cells and the roles of critical Ca²⁺ regulatory proteins in differentiating cardiomyocytes and neuronal cells from ES cells (*Proc Natl Acad Sci USA* 2002; 99: 9225-9230; *FASEB J* 2006; 20: 181-183; *Cell Calcium* 2007; Epub ahead of print).
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Dr. TANG Chao-Shu received his B.S. degree in medicine in 1968 and M.S. degree in Pathophysiology in 1981 from Beijing Medical College, respectively. As a visiting scholar he moved to Saint Louis University to continue his research work during 1985.6-1986.7, 1989.5-1990.5, 1993.3-1994.10, 1997.8-1998.4, respectively. He was promoted to be a professor in 1990 and to be a post-student supervisor in 1993, respectively. Professor TANG has been engaged in teaching and research work of physiological and pathological mechanisms of cardiovascular system. The long-term goal of Professor TANG’s laboratory is to be elucidating vasoactive peptide mechanisms of cardiovascular disease pathogenesis and cellular protection mechanisms against cardiovascular diseases. He was a chief scientist of the State Major Basic Research Development Program of China “973” (2000-2005). He took charge of the Major Program of National Natural Science Foundation of China and State Major Science and Technology Program of the Science and Technology of China (“85” and “95” program). He is Associate Editor-in-Chief of journals including “Acta Physiologica Sinica”, “Progress in Physiological Science”, “Journal of Peking University (Health Sciences)”, “Chinese Journal of Arteriosclerosis”, etc. And he is an editor of journals including “Chinese Medical Journal” and “Chinese Journal of Cardiology”, etc. As a chief editor, He wrote many books including “Pathophysiology”, etc. So far, he has published more than 100 original research papers collected in Science Cited Index (SCI). The major awards he has been granted include a Second-class National Prize for Progress in Science and Technology and more than 20 awards at the ministerial (provincial) level.