Editorial

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Mitochondrial Metabolic Inhibition and Cardioprotection

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Reperfusion is needed to initiate reflow of blood in cardiac arrest triggered by surgical intervention or pathologically-induced cardiac ischemia. However, subsequent reperfusion may lead not only to the recovery of ischemic cardiac tissue, but also to the paradoxical phenomenon of myocardial ischemia/reperfusion (IR) injury, including protracted organ recovery, myocardial stunning, and acute myocardial infarction (MI). Mortality due to acute MI remains substantial, and the prevalence of MI-associated heart failure is increasing worldwide.[1] The year 2016 is the 30th anniversary of the first report of ischemic preconditioning (IPC) by Murry, Jennings, and Reimer, and elucidation of the signaling pathways underlying IPC has led to the discovery of various therapeutic targets for pharmacological cardioprotection.[1] It is increasingly evident that the cardioprotective paradigms of IPC and ischemic post-conditioning employ modulation of mitochondrial oxidative metabolism as a key effector mechanism because mitochondria can act as inducers of reperfusion injury or effectors of cardioprotection.[1][2]

Mitochondria are specialized organelles that generate adenosine triphosphate (ATP) via the electron transport chain and the oxidative phosphorylation system and are essential for maintaining energy homeostasis in cardiomyocytes. Therefore, mitochondria are major determinants of cell survival or death. During reperfusion, ischemically damaged mitochondria further increase oxidative damage, calcium-driven myocyte injury, and the activation of apoptotic programs.[1] The cardioprotective effects observed following pharmacological blockade of mitochondrial respiration during IR clearly show the contribution of ischemic mitochondrial damage to myocardial injury after reperfusion.[2] Given that mitochondrial respiration is already inhibited during hypoxia or ischemia, it is surprising that several respiratory inhibitors[3] or IPC can improve recuperation from IR injury (Fig. 1). Reversible inhibition of mitochondrial metabolism may offer protection during reperfusion by facilitating a gradual restoration of mitochondrial function, i.e., a slow reintroduction of electrons into the respiratory chain following reperfusion.[3] In strategies modulating mitochondrial respiration, pharmacological agents such as amobarbital, rotenone, and s-nitrothiols can offer protection against IR injury by inhibiting mitochondrial Complex I (nicotinamide adenine dinucleotide phosphate ubiquinone oxidoreductase). However, unlike the direct association of cardioprotection with the inhibition of Complex I, the cardioprotective effect of some agents, including ranolazine, capsaicin, volatile anesthetics (halothane and isoflurane), menadione, and metformin may be dependent on their effect on Complex I (Fig. 1). There are two suggested modes of cardioprotection via Complex II. The first is direct inhibition of Complex II by 3-nitropropionic acid, malonate, and nitric oxide. The second mode involves the opening of a putative mitochondrial ATP-sensitive potassium channel.[1][3] Although inhibition of either Complex I or II alone could, theoretically, be by-passed by feeding electrons through the other complex, inhibition of Complex III leads to a complete blockage of the respiratory chain and does not provide cardioprotection. Complex IV (cytochrome c oxidase) is a dimeric enzyme comprising 13 subunits per monomer, and it is strictly regulated by the availability of substrate, interference with the catalytic cycle, multiple allosteric modulation, and covalent posttranslational modifications.[4] Therefore, Complex IV is referred to as the pacesetter of mitochondrial oxidative metabolism and ATP synthesis. Four gaseous molecules, namely, nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H_2S), and cyanide (CN), directly

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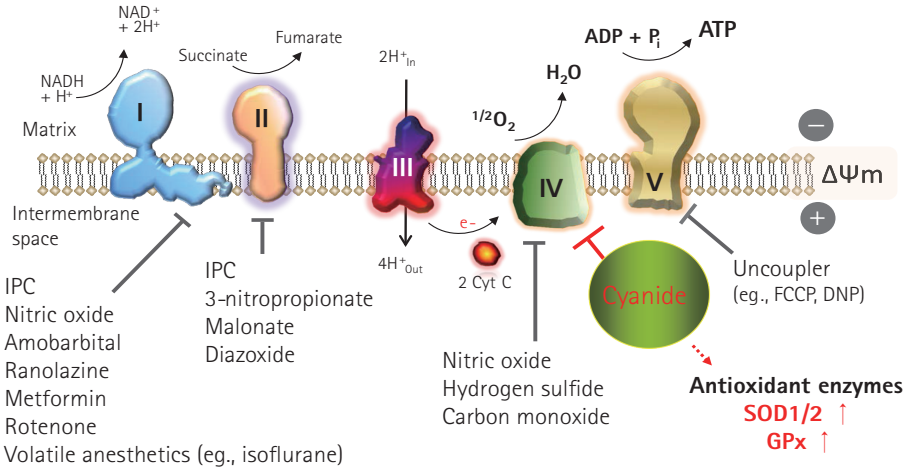

Fig. 1. Inhibition of mitochondrial complexes involved in cardioprotection. I–V indicate respective mitochondrial complexes. NADH: reduced nicotinamide adenine dinucleotide, NAD^+: oxidized nicotinamide adenine dinucleotide, ADP: adenosine diphosphate, Pi: inorganic phosphate, ATP: adenosine triphosphate, ΔΨm: mitochondrial membrane potential, IPC: ischemic preconditioning, Cyt C: cytochrome C, FCCP: carbonyl cyanide-p-trifluoromethoxyphenylhydrazone, DNP: dinitrophenol, SOD: superoxide dismutase, GPx: glutathione peroxidase.

inhibit this complex by interfering with the catalytic cycle or by binding at distal allosteric sites.[3)5)] The mechanisms of Complex IV inhibition by NO and CO are dependent on oxygen concentration, but those of CN and H_2S are not.[3)5)] Surprisingly, although antitumor anthracyclines such as daunomycin and doxorubicin also inhibit Complex IV activity, they are not cardioprotective. In the case of Complex V (ATP synthase), the protective effect of mitochondrial respiration uncouplers against IR injury is only observed across a narrow concentration range, and more severe uncoupling of Complex V results in mitochondrial depolarization and cell death.

Gasotransmitters are small gaseous molecules with important physiological functions.[5)] CO, NO, and H_2S can be endogenously produced (Table 1) and have been shown to ameliorate IR injury by inducing a number of cytoprotective mechanisms, including modulation of mitochondrial respiration, induction of vasodilatation, inhibition of apoptosis, stimulation of antioxidant activity, and inhibition of inflammation.[5)] CN is another inhibitor of Complex IV and exists as a salt, liquid, or gas. Unlike the other three gasotransmitters, CN cannot be endogenously produced, and its role as a gaseous signaling molecule is not well known. Recently, application of low-dose CN to an experimental IR model has been reported.[6)] Pretreatment with CN reduced infarct formation during IR and well preserved left ventricular contractility. However, CN treatment could upregulate superoxide dismutase 1 and 2 and glutathione peroxidase, which are important mitochondrial antioxidant enzymes.[6)] This finding strongly suggests that CN could be used as a shield for reducing IR injury by targeting Complex IV. In addition to its role in cardioprotection, elucidating the physiological role of CN as a gasotransmitter will be valuable in understanding cardiovascular complications. Further research on safer delivery of gasotransmitters to the cardiovascular system is therefore recommended.

Despite extensive efforts spanning several decades to translate the knowledge on cardioprotection into clinical practice, no cardioprotective drugs are commercially available, and no therapeutic interventions are easily accessible for routine clinical

Table 1. Representative characteristics of gasotransmitters

Gasotransmitter	Enzymes involved in production	Half life (in vivo)	Signaling pathway involved
NO	NOS; endothelial, neuronal, and inducible	Seconds	• Anti-inflammation • Anti-apoptosis • NRF2-mediated-antioxidant • Vasorelaxation • Cardioprotection
CO	HO-1, -2, and -3	Minutes	
H_2S	Cystathionine β-synthase Cystathionine γ-lyase Cysteine aminotransferase and 3-Mercapto-pyruvate sulfurtransferase (mitochondria)	Seconds	

NO: nitric oxide, CO: carbon monoxide, H_2S: hydrogen sulfide, NOS: nitric oxide synthase, HO: heme oxygenase, NRF2: nuclear factor E2-related factor-2

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application.[1] However, it would be premature to abandon research on cardioprotection by pharmaceutical conditioning.[7] In addition to signaling pathways and metabolic changes involved in ischemic pre-, post-, and remote conditioning,[1][7] the development of a strategy for reversible mitochondrial inhibition may be valuable and promising in reducing cardiac IR injury.[6][8] However, even a single cell does not contain a homogenous pool of mitochondria; therefore, the outcomes of such an approach will not be uniform. Gasotransmitters such as NO, CO, H_2S, and CN are powerful inhibitors of Complex IV, and their application as cardioprotectants will lead to novel strategies for developing cardioprotective drugs. The use of mitochondrial inhibitors is also a safety concern because they may produce unexpected or severe side effects, including neurotoxicity. Therefore, it is necessary to develop tools for controlled and targeted delivery of identified cardioprotective compounds to the mitochondria. In therapeutic regimens, reperfusion therapy using a combination of identified agents differently targeting IR injury will be another attempt at decreasing the severity of myocardial infarction.[1] This is necessary because IR injury cannot be attributed to a single cause and, therefore, cannot be efficiently prevented by a single agent.

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