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EDITORIAL COMMENT

A novel cardioprotective strategy targeting mitochondrial reactive oxygen species production independent of antioxidant activity

Uma nova estratégia cardioprotetora que reduz a produção de ROS mitocondrial independente da atividade antioxidante

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Ischemic heart disease is the leading cause of death worldwide. Chronic or acute occlusion of a coronary artery results in a shortage of oxygen and nutrient supply to some areas of the heart, leading to dramatic myocardial remodeling that includes disturbances of electrical conduction, cardiomyocyte death, inflammation and fibrosis.[1,2] In most cases, the therapeutic strategy involves primary percutaneous coronary intervention (PCI) in order to open up the obstructed coronary artery and restore blood flow. The clinical decision to proceed with PCI is based on the patient's electrocardiographic profile and levels of circulating markers at the time of diagnosis that denote the presence of cardiac lesion. It is therefore of the utmost importance to identify new blood markers that reveal mechanisms of cardiomyocyte injury.[3] Cardiac imaging modalities such as positron emission tomography are also important for assessing the myocardial perfusion profile, which reflects the extent of the damage, helping to establish an accurate prognosis as well as the most appropriate therapeutic approach to improve patient outcomes.[4]

Although reperfusion by PCI remains the gold standard for treating ischemia-related injury, it is often associated with excessive production of reactive oxygen species (ROS), inducing exacerbated oxidative damage, which results in apoptosis-mediated death of cardiomyocytes, a phenomenon known as ischemia-reperfusion injury. Various strategies have been tried to reduce ischemia-reperfusion injury. Ischemic conditioning, stem cell therapies and aerobic exercise are among the most common non-pharmacological approaches following myocardial infarction. A recent study showed that aerobic exercise training enhances the beneficial effects of stem cell therapy in the left ventricle of rats with moderate infarction, likely inhibiting cardiomyocyte apoptosis.[5] Alternatively, pharmacological therapies are often designed to prevent the production of ROS and/or to boost the endogenous antioxidant defenses of cardiomyocytes.

In their study published in the current issue of the *Journal*, Weng et al.[6] show that dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist, prevents H_2O_2-induced apoptosis of cardiomyocytes by reducing ROS formation. The cardioprotective role of dexmedetomidine has previously been noted: several studies have reported that dexmedetomidine effectively attenuates cell injury and apoptosis, by reducing mitochondrial dysfunction. Surprisingly, in the manuscript by Weng et al.,[6] evidence is provided that the cardioprotective effect of dexmedetomidine is not mediated by increased expression

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of antioxidant enzymes. Thus, it is conceivable that the effect of dexmedetomidine on ROS production is exerted on the mitochondria, the main source of endogenous ROS. For example, reduced mitochondrial membrane potential depolarization was previously observed after dexmedetomidine treatment of H_2O_2-induced oxidative stress injury in cardiomyocytes,[7] while dexmedetomidine-mediated activation of mitochondrial ATP-sensitive potassium (mitoKATP) channels contributed to neuroprotection in a cerebral ischemia-reperfusion injury model.[8] Mitochondrial ROS are crucial mediators of apoptosis. However, lower levels of ROS are also important to ensure signaling of important cellular processes, such as autophagy and transcriptional activation, and are essential for the protective effects of ischemic conditioning in the heart. In line with this idea, molecules targeting both the activation of mitoKATP channels and ROS generation, such as diazoxide, have been considered viable cardioprotection strategies. Interestingly, the protective effect of diazoxide is lost in connexin43 (Cx43)-deficient cardiomyocytes, which is consistent with an important role of mitochondrial Cx43-dependent production of ROS.[9] Although classically associated with gap junction channel-mediated communication and propagation of electrical impulses throughout the heart muscle, localization of Cx43 in mitochondrial membranes has been implicated in the regulation of mitochondrial ion homeostasis, morphology and oxidative metabolism. Importantly, mitochondrial Cx43 levels increase during ischemic preconditioning, likely helping to keep the mitochondrial permeability transition pore in a closed state, delaying the release of apoptotic proteins and preventing cell injury.[2] Moreover, the lack of mitochondrial Cx43 prevents the cardioprotective effect of ischemic preconditioning. Nonetheless, the mechanisms and molecular players underlying the trafficking of Cx43 to the mitochondria under physiological and pathological conditions, as well as the exact roles of mitochondrial Cx43, remain unclear.

Excessive oxidative damage caused by ROS-induced ROS release, in which ROS trigger opening of mitochondrial permeability transition pores or anion channels, has been implicated in mitochondrial membrane potential collapse with a consequent increase in ROS generation. Given its putative role as a mitochondrial channel and its association with proteins of the mitochondrial respiratory chain, it is plausible that the effect of dexmedetomidine in reducing ROS production is due to its impact on mitochondrial Cx43. In line with this idea, several studies have shown that dexmedetomidine affects Cx43 homeostasis. For example, it was shown that upregulation of Cx43 mediates the antiarrhythmic effect of dexmedetomidine in ischemic cardiomyopathy, reducing fibrosis and inflammation.[10] Another study demonstrated that dexmedetomidine-induced protection against cardiac ischemia-reperfusion injury involves Cx43 and activation of large-conductance $Ca2^+$-sensitive potassium channels.[11] Moreover, it has been suggested that upregulation of astrocyte Cx43 by dexmedetomidine attenuates brain ischemia-reperfusion injury.[12]

Altogether, the manuscript by Weng et al. is a valuable contribution, demonstrating that dexmedetomidine administration constitutes a potential therapeutic strategy to reduce mitochondrial ROS production in injured cardiomyocytes, which appears to be independent of antioxidant enzyme expression levels. These results may broaden the discussion about alternative protective mechanisms triggered by dexmedetomidine, including via direct impact on the activity of mitochondrial channels.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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