NADPH oxidase: short-term foe, long-term friend

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In this issue of Journal of Applied Physiology, Nottin and colleagues (9) in their manuscript “β-Adrenergic receptors desensitization is not involved in exercise-induced cardiac fatigue; NADPH oxidase-induced oxidative stress as a new trigger,” examine the involvement of both β-adrenergic pathway and NADPH oxidase (Nox) 37 enzyme-induced oxidative stress on the development of myocardial dysfunction following exposure to prolonged exercise in a rat model.

Cardiovascular adaptations and responses to endurance exercise have been a major area of interest to clinicians and physiologists for the past century. Due to the increasing popularity and advances in cardiovascular imaging technology, the ability to accurately assess the dynamic state of cardiovascular structure and function has improved exponentially over the past two decades. Numerous biochemical and physiological changes in response to both short- and long-term exercise have been described; however, the ability to better understand the underlying mechanisms responsible for these changes have remained elusive.

Numerous authors have described structural and biochemical evidence of possible myocardial insult in association with endurance exercise (5, 7). Echocardiographic evidence of structural and physiological abnormalities associated with endurance exercise include impaired diastolic and systolic function, elevated estimated pulmonary arterial pressures, and right ventricular dilatation and dysfunction (4, 5). Biochemical evidence of myocardial perturbation includes the well-documented association between prolonged endurance exercise and increased troponin levels following exercise. Mechanisms responsible for this finding include a reversible increase in the membrane permeability of cardiomyocytes and release of troponin from the cytoplasmic pool, elevated catecholamines, oxidative stress and effect of free radicals, alteration in myocardial cellular metabolism, and possible loss of myocardial cellular membrane structural integrity. A recently published study used magnetic resonance imaging following completion of a marathon and found no evidence of myocardial injury despite elevated levels of cardiac biomarkers. These authors described prolonged endurance exercise as leading to myocardial “overstimulation” (3).

Dr. Nottin and colleagues sought to determine the role of the β-adrenergic pathway in the cardiovascular response to prolonged exercise. Moreover, other underlying mechanisms involving oxidative stress have been recently proposed. The present study aimed to evaluate the involvement of both the β-adrenergic pathway and NADPH oxidase (Nox) enzyme-induced oxidative stress in myocardial dysfunction in rats following prolonged exercise. Consistent with the prior studies in humans, in this animal model, the authors found evidence of decreased left ventricular systolic and diastolic function as well as elevation of plasma troponin I. The authors concluded that the observed myocardial dysfunction following exercise was due to oxidative stress and not adrenergic desensitization. These findings are of particular interest in that they may in part explain some of the training effect-resilience to detrimental cardiac effects of repeated exposure to endurance exercise and may be helpful in identifying potential therapeutic agents that can prevent the damaging effect of free radical exposure both in the endurance exercise setting as well as in other clinical states in which NADPH oxidase is activated. Of note, the animals studied in this particular manuscript had not been exposed to chronic training, thus the functional and biochemical response are similar to those identified in exercise naïve subjects. Several studies have demonstrated evidence of greater biomarker (troponin and NH2-terminal Pro BNP) release in less trained subjects (2, 5).

Reactive oxygen species produced during exercise are thought to act as second messengers and aid the development of ischemic preconditioning with the mitochondria implicated as the primary source of reactive oxygen species (ROS) during preconditioning (1, 6). Sanchez and colleagues (6) examined the effect of NADPH oxidase on ryanodine receptor-2 (RyR2) S-glutathionylation and the preconditioning effect of exercise and tachycardia on infarct size following occlusion of a coronary artery in a canine model. They concluded that NADPH oxidase inhibitor was instrumental in the induction of cardioprotection and that ROS generated by this enzyme are important mediators of the preconditioning response. Inhibition of NADPH oxidase by apocynin prevented the increase in RyR2 S-glutathionylation, decreased calcium release activity, and negated the protective effects of preconditioning through exercise and tachycardia on infarct size.

This manuscript is providing the first link in the chain of events that transpires following exposure to exercise. The authors have very elegantly identified the role of NADPH oxidase in the development of biochemical and structural effects of exercise. It is possible that prolonged exposure to these adverse conditions provides the substrate for the development of multiple adaptive cellular pathways that protect from the effects long term and are a critical component of the training effect.

REFERENCES

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