New insights: Does heat shock protein 70 mediate exercise-induced cardioprotection?

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ACROSS SEVERAL MAMMALIAN SPECIES, moderate to high intensity aerobic-type exercise consistently protects against experimental ischemia-reperfusion (IR) insults by mitigating IR-induced ventricular arrhythmias, pump dysfunction, and tissue death [see review (8)]. Collective understanding of exercise-induced cardioprotection against IR injury was significantly advanced by the observation that a few days of moderate intensity treadmill exercise elicited levels of cardioprotection comparable to those of an extended exercise regimen, i.e., exercise training lasting weeks to months (1, 8). The short-term time course for inducing resistance to IR injury suggests the phenotype is independent of ventricular or vascular remodeling and implicates acute upregulation of cardioprotective factors. Heat shock proteins (HSP) are among the various biochemical factors suspected as mediators of exercise-induced cardioprotection.

Several important observations underpin early investigations of HSPs as potential mediators of exercise-induced cardioprotection, the foremost being that HSPs are readily inducible within hearts of animals exposed to a short-duration exercise regimen (1, 2, 6). Although limited evidence suggests several members of the HSP family, including Hsp40, Hsp70, and Hsp90, are upregulated in hearts of short-term exercised animals, only the HSP70 family is consistently overexpressed in the exercised phenotype (2, 5, 6, 9, 11). In regard to the HSP70 family of proteins, nomenclature often delineates between the exercise inducible 72-kDa Hsp72 and the constitutive 73-kDa HSP73. Cardiac overexpression of Hsp70 in exercised hearts is currently verified relative to exercise-induced thermogenesis and reactive oxygen species production, but not hemodynamic overload (3, 10). A regimen of short-term treadmill exercise in Sprague-Dawley rats elicits between 1.5- and 7-fold increases in cardiac Hsp70 content, a response that is generally proportional to the magnitude of the increase in core temperature during exercise (2, 3, 5, 9, 11). Given the association between cardiac Hsp70 upregulation and the robust cardioprotection observed in exercised hearts, many researchers have postulated that a causative relationship must exist. This rationale was underscored in a study by Hutter et al. (4) in which groups of Sprague-Dawley rats were passively heated to a core temperature of 40, 41, or 42°C prior to experimental IR injury induced by coronary artery ligation in vivo. Their results demonstrated an inverse correlation in the mean responses for cardiac Hsp72 content and infarct size ($r = -0.97, P = 0.037$) (4).

In 1999, Taylor et al. (11) performed the first reductionist study of HSP70 family upregulation and exercise-mediated cardioprotection. In their investigation of hearts from Sprague-Dawley rats, an almost sevenfold increase in cardiac Hsp72 content was elicited via the hyperthermic response to either 1 day or 3 consecutive days of treadmill exercise. In a third group, cardiac Hsp72 upregulation was prevented by maintaining basal core temperatures during a single bout of treadmill exercise performed at an identical intensity and duration in a cold environment (8°C). Rat hearts from all groups were later exposed to global IR using an isolated perfused working heart apparatus to determine if attenuation of Hsp72 content was matched by a loss in exercised-induced cardioprotection. Intriguingly, the results did not support an essential role for Hsp72 as a mediator of exercise-induced cardioprotection in that, independent of cardiac Hsp72 content, all exercised hearts exhibited cardioprotection against ventricular contractile deficits caused by the global infarct (11). Follow-up studies used a similar approach (exercise in a cold environment) to prevent Hsp72 overexpression in rat hearts prior to surgically controlled IR in vivo (2, 9). Hamilton et al. (2) were the first to observe that hearts from rats exercised in cold or warm environments were equally protected against IR-induced tissue necrosis, suggesting that Hsp72 is not essential for the tissue sparing effects of exercise. Quindry et al. (9) subsequently confirmed this necrotic-sparing observation and further demonstrated that anti-apoptotic protection associated with exercise was also independent of cardiac Hsp72 overexpression. A separate study by Hamilton et al. (3) used a diet fortified with an antioxidant cocktail to prevent Hsp72 overexpression in exercised hearts. Similar to the cold environment studies, exercised rats fed the antioxidant enriched diet failed to overexpress cardiac Hsp72. Nonetheless, prevention of Hsp72 upregulation in exercised hearts of antioxidant fed rats did not mitigate cardioprotection against IR-induced tissue necrosis (3). Collectively, these studies led to the working assumption that upregulation of HSP70 family proteins is not essential to exercise-induced cardioprotection against IR injury (8).

The aforementioned conclusion that Hsp70 does not mediate exercise-induced cardioprotection has been challenged by exciting new data published in this issue of the Journal of Applied Physiology. Milne et al. (7) provide a novel approach to understanding inducible Hsp70 overexpression in exercised hearts. In their study, male Sprague-Dawley rats were exposed to 1 or 5 days of short-term exercise. Control animals remained sedentary in normo- or hyperthermic conditions. In all groups, Hsp70 content was examined in hearts excised from anesthetized animals 30 min to 24 h following each experimental treatment condition. Similar to previous research, Western blot analyses in this study revealed a six- to sevenfold increase in Hsp70 content in hearts 24 h after 1 or 5 days of treadmill exercise. However, closer inspection of ventricular cross sections using confocal microscopy revealed for the first time that Hsp70 overexpres-

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This important discovery by Milne et al. (7) raises new questions about whether Hsp70 may, in fact, mediate exercise-induced cardioprotection through improvements in coronary blood flow during IR. Relative to this new observation, prior research by Taylor et al. (11) examined total coronary flow in their isolated perfused working heart experiments, but did not find that cardioprotective differences were attributable to exercise or increased cardiac Hsp70 content. However, these findings do not rule out a potential role for Hsp70. The reason is that perfusates with no hemoglobin and high O2 partial pressures in isolated heart preparations induce nonphysiological coronary vasodilation, thus making it impossible to draw conclusions about coronary flow within that experimental context. Moreover, given recent understanding that mechanisms of exercise-induced cardioprotection are unique to the form of IR injury (arrhythmia, ventricular stunning, and tissue death) (8), there is further cause to once again question whether Hsp70 is essential to exercise-induced cardioprotection. Future investigation of animal models in vivo is needed to reveal whether Hsp70 overexpression may in fact mediate exercise-induced cardioprotection against IR injury through vasodilatory responses.

In conclusion, short-term exercise is associated with a robust increase in cardiac Hsp70 content and concomitant cardioprotection against IR injury. Whether these two observations are independent responses to the exercise stimulus or a mechanistically integrated cause and effect remains undetermined. By the use of confocal microscopy to confirm the tissue specific location of Hsp70 overexpression in exercised hearts, the findings of Milne et al. (7) raise new questions about a relatively well-studied area of physiology. This approach is a sobering reminder of the need to confirm physiological conclusions with definitive secondary biochemical, histological, and molecular biology techniques when examining mixed tissue organs such as the heart.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

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