Exercise-induced cardiac preconditioning: how exercise protects your achy-breaky heart

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Frasier CR, Moore RL, Brown DA. Exercise-induced cardiac preconditioning: how exercise protects your achy-breaky heart. J Appl Physiol 111: 905–915, 2011. First published March 20, 2011; doi:10.1152/japplphysiol.00004.2011.—The ability of exercise to protect the heart against ischemia-reperfusion (I/R) injury is well known in both human epidemiological studies and experimental animal models. In this review article, we describe what is currently known about the ability of exercise to precondition the heart against infarction. Just 1 day of exercise can protect the heart against ischemia/reperfusion damage, and this protection is upheld with months of exercise, making exercise one of the few sustainable preconditioning stimuli. Exercise preconditioning depends on the model and intensity of exercise, and appears to involve heightened oxidant buffering capacity, upregulated subunits of sarcolemmal ATP-sensitive potassium channels, and adaptations to cardiac mitochondria. We review the putative mechanisms involved in exercise preconditioning and point out many areas where future research is necessary to advance our understanding of how this stimulus confers resistance against I/R damage.

THE BENEFITS OF EXERCISE in promoting health are well documented throughout human history. Various forms of exercise were prescribed by the ancient Chinese, Indians, Greeks, and Romans, making exercise arguably the oldest therapeutic intervention for the treatment or prevention of disease (80). As our understanding of the cardiovascular system evolved, so too did the notion that the overall health of the cardiovascular system could be improved with exercise. Beginning as early as the 1850s exercise was prescribed specifically for the prevention of heart disease in Scotland and Scandinavia, and later in the mountain resorts of Germany (80). In the United States, the public health pioneer Dr. James M. Anders was among the first to recognize the beneficial effects of exercise medicine. In a 1904 speech, Anders noted that, “It should ever be a feature of our therapeutic creed, to give close attention to physiologic means and to recognize their superiority over drugs as curative agencies” (3).

Fast forward a century, and one will find an obesity and diabetes epidemic sweeping through industrialized nations, with physical inactivity now recognized as a major risk factor for cardiovascular disease. Recent estimates suggest that ~12% of the cost of cardiovascular disease can be attributed to physical inactivity (138), making physical inactivity a multibillion dollar problem. A significant amount of time, effort, and resources are being devoted to preventative methods seeking to reduce the burden that ischemic heart disease places on both our species and our health care system. In this review article, we seek to summarize the current literature regarding the ability of exercise to delay/reduce cardiac ischemia-reperfusion injury; in short, we will describe how exercise can make “achy” hearts a little less “breaky.”

Before we begin, it should be noted that exercise is known to reduce arrhythmia (48, 97, 114), decrease myocardial stunning (14, 82), and improve coronary vascular reactivity (18, 72, 73) in hearts exposed to ischemia-reperfusion (I/R). Several recent papers have discussed exercise cardioprotection (5, 9, 110, 111, 120), and many of these articles have focused on other indexes of ischemic injury besides cell death. In this minireview, we will focus almost exclusively on the ability of exercise to confer resistance against infarction. In the first half of this review, we provide a comprehensive overview of the exercise type, duration, and intensity needed to protect the heart. In the second half, we discuss underlying cellular mechanisms responsible for exercise cardioprotection. We highlight new insights into how exercise may trigger and mediate pro-
estion against infarction, and we discuss the time course of cellular events during ischemia and reperfusion that may be altered in the heart after exercise. Finally, throughout this review we point out areas where future research can augment our understanding of exercise-induced cardioprotection.

CAN WE REALLY “PRECONDITION” THE HEART AGAINST INFARCTION?

In the scientific literature, a growing number of strategies have been found to protect the heart from I/R injury. Among the first of these strategies is the “preconditioning” phenomenon, first noted by Murry et al. (94), where short ischemic episodes before a long index ischemia decreased infarction. A number of stimuli have subsequently shown to precondition the heart against injury (reviewed in 11), along with the recent discovery that slowly bringing the heart out of ischemia with “postconditioning” also salvages myocardium (131). Pre-/post-conditioning delays the onset of I/R injury, but the extent of protection depends critically on the establishment of reperfusion. In the clinic, prompt reperfusion remains the best treatment to salvage tissue, and in experimental settings pre-/postconditioning stimuli lose their efficacy to reduce injury with prolonged ischemia (94, 103, 137). However, the reestablishment of coronary flow induces problems of its own (reperfusion injury, discussed below), and we will address the etiology of injury during both ischemia and reperfusion.

Naturally, there is enormous interest in trying to “mimic” ischemic pre-/postconditioning with a compound administered to patients hospitalized for ischemic events. Despite scores of potential treatments that are effective in experimental settings, to date none of the putative compounds have been incorporated into clinical standard of care. The reasons for the lack of translation have been well described elsewhere (40), but the correlation between humans who exercise and reduced morbidity/mortality after infarction is well documented.

WHAT IS THE RELATIONSHIP BETWEEN EXERCISE AND INFARCT SIZE?

Epidemiological evidence has indicated that there is a strong correlation between individuals who exercise regularly and those who survive a myocardial infarction (92, 104–108). Elderly humans who are sedentary appear to lose the preconditioning benefits of preinfarction angina, although the protection was seen in counterparts who exercised (1, 116). Given the relationship between infarct size and mortality (50, 88), exercise is postulated to promote survival by delaying cell death during metabolic challenge, reducing the mass of infarcted tissue.

Although direct confirmation of exercise-induced infarct sparing is difficult to measure in human hearts, several studies have provided indirect evidence of exercise cardioprotection in the human heart. Zdrenghea et al. (139) found that exercise-induced ST-segment depression was significantly attenuated in the human heart. Zdrenghea et al. (139) found that exercise-induced ST-segment depression was significantly attenuated in

human heart tissue, as forearm exercises improved ischemic function in isolated human atrial trabeculae (117).

Exercise-induced reductions in infarct size have been observed across animal models, corroborating human epidemiological data. The first observation of exercise cardioprotection was noted 8 years before the discovery of ischemic preconditioning (IPC) (86), and has been observed in both male (2, 20, 25, 28, 43, 51, 134, 135) and female (17, 18, 20, 28, 49) animals. Infarct salvage can be seen using both in vivo (2, 43, 49, 51, 135) and ex vivo (perfused heart) (17, 18, 20, 25, 28, 35, 138) preparations of I/R, indicating that both systemic and intrinsic cardiac adaptations are likely responsible for the protective phenotype. Although most studies have used younger animals, the exercise-induced cardioprotection appears to be upheld with aging (75, 112, 122). This distinction is important, as the vast majority of deaths from myocardial infarction occur in humans over the age of 65.

On average, the magnitude of protection evoked by exercise preconditioning is a 30–40% reduction in injury (reviewed in more detail in 21). This magnitude in infarct size reduction is consistent with many pharmacological treatments aimed to decrease injury, but does not appear to be as large in magnitude as classical ischemic preconditioning (137).

IS EXERCISE REALLY THE SAME AS “PRECONDITIONING”?

There are a number of similarities between exercise-induced cardioprotection and other preconditioning stimuli. The time course for protection is very similar across models, with a narrow first window of robust protection followed by a “second window” of more modest protection (38, 135, 137). In both IPC and acute exercise preconditioning, infarct size is significantly lower within 1 h of the stimulus, but this protection wanes for ~24 h. A second window of protection is observed following both IPC and exercise preconditioning, and in both cases the second window reflects a much wider time frame to observe a preconditioning effect (approximately 24–36 h after the preconditioning stimulus).

The only studies to examine the time course for exercise preconditioning used a single bout of exercise (38, 135). Repetitive exercise training over weeks/months evokes a number of morphological/phenotypic changes in the myocardium, including resting bradycardia, hypertrophy of the left ventricle, cellular growth/adaptations in cardiac myocytes, and altered coronary vascular function (17, 18, 75, 86). These changes make it a little more difficult to compare a chronic stimulus with acute stimuli such as classical ischemic preconditioning, and future studies looking to compare the time course for protection following chronic training hope to provide insight into whether the protection is still characterized by two distinct windows of preconditioning.

Although exercise may share some of the mechanistic pathways with IPC (e.g., a role for reactive oxygen species; covered in detail below), there are clear distinctions. For example, phosphorylation of Akt or GSK-3β has been observed in a number of preconditioning models (reviewed in 93), but neither Akt nor GSK-3β phosphorylation appear to be necessary for exercise cardioprotection (17, 30). Furthermore, increased cyclooxygenase-2 (COX2) is seen in several preconditioning models (13), but upregulated COX2 was not found to be involved in exercise preconditioning (113).
Several other characteristics of exercise preconditioning distinguish this preconditioning stimulus from the others. First, any preventative treatment must be shown to be sustainable for long periods of time. Many experimental stimuli appear to “precondition” the heart when given one time, but unless our powers to forecast impending coronary events improve drastically, the clinical relevance of one-time administration of preventative measures must be questioned. As a preventative measure, exposure to exercise protects the heart against infarction after either 1 day, or many months of the exercise stimulus. Second, any potential therapy must be readily available to patients, and there is no treatment that is more readily available to patients (or more economically affordable) than exercise. Finally, as addressed above the epidemiological evidence is clear that exercise is also protective to human hearts. Given these distinctions from classical models of preconditioning, exercise is arguably the most clinically relevant preconditioning stimulus that has been studied to date. With such enormous potential, we will now address how much of this stimulus is necessary to precondition the myocardium.

HOW MUCH EXERCISE IS NEEDED TO PROTECT THE HEART?

An interesting (and on-going) challenge is to determine exactly how much exercise is needed to evoke protection against I/R injury. By far, the most common exercise model in the literature is forced treadmill running in the rat. In most studies, 30–60 min of running at treadmill speeds of 27–33 m/min is used as the exercise stimulus (often bookended by 10–15 min of lower-intensity running at ~15 m/min). Such protocols consistently confer protection against infarction (see below) and reflect an exercise intensity of ~75% of maximal oxygen consumption (V\textsubscript{O\textsubscript{2max}}) (6). To the best of our knowledge, the influence of lower-intensity treadmill running (~60% V\textsubscript{O\textsubscript{2max}}) on infarct salvage is not known. Studies examining postischemic mechanical recovery after lower-intensity treadmill running protocols have found equivocal results, with some finding improved recovery with exercise (78), and others finding no effect (121). A direct relationship between exercise intensity/duration with infarct salvage must be addressed in future studies.

Unlike skeletal muscle, training adaptations to the heart following treadmill protocols are not normally characterized by increased Krebs cycle intermediates [citrate synthase, for example, is not normally increased in trained hearts (71, 98, 109)], but there are training adaptations such as increased antioxidants (covered in detail below) and left ventricular hypertrophy. The resting bradycardia induced by higher-intensity treadmill running can even be observed in the isolated heart (17), indicating that intrinsic adaptations to pacemaker currents may also accompany altered autonomic nervous system tone.

Our best insight into how much exercise is needed is provided by studies that have used different models, intensities, and durations of exercise and looked at increased expression of cardioprotective proteins (such as cellular antioxidants and/or heat shock proteins). An exercise intensity of ~24 m/min (with a treadmill incline ~2%) appears to be necessary for the upregulation of myocardial heat shock proteins (89, 98), although several studies have dissociated the link between exercise-induced protection and elevated heat shock proteins (47, 121, 126). Increased manganese superoxide dismutase (MnSOD) is observed in young animals following exercise at intensities ~27 m/min with treadmill incline set at either 0% (44, 51, 114, 135) or 10% (18, 25). Increased cardiac MnSOD can be induced at lower treadmill speeds (20–25 m/min) if a treadmill grade of ~10% is applied (52, 115), but is not observed at treadmill speeds < 20 m/min (27, 78).

Future research that determines how long exercise cardioprotection persists after cessation of an exercise regimen will also improve our understanding of exercise preconditioning. Although no study has directly determined how long exercise-induced infarct salvage lasts after stopping exercise, an interesting study from Powers’ group (77) investigated the effects of exercise cessation on functional recovery. In their study, Lennon et al. (77) exercised animals for a total of 8 days, with the final 3 days consisting of high-intensity exercise (30 m/min for 1 h). The beneficial effects of exercise (as evidenced by postischemic recovery of cardiac work) persisted for 9 days after cessation of the exercise, but by 18 days postexercise there was no longer an exercise effect.

While the cardioprotective benefits of treadmill running protocols are clear, the limitations of this model must be clearly recognized. Animals that do not run on the treadmill are often prodded, blasted with air, or shocked via an electrical grid. The caveat that animals may display a stress response following this “motivation” must be acknowledged in forced treadmill studies, especially those where exercise only lasts a few days. Only a few investigators have attempted to address this issue, and in both cases there was evidence (especially in male animals) of systemic stress (reflected by adrenal hypertrophy, splenic atrophy, and increased circulating corticosterone) (19, 91). Admittedly, these data are subject to different interpretations (what is “stress” vs. “exercise adaptations”?), and we hope that the dialogue regarding the best experimental exercise approach will continue among scientists in this field.

More work must be done to determine if voluntary wheel running protocols can protect the heart against infarction. Wheel running has the advantage that animals run ad libitum, with rats often covering several kilometers per day (76). The disadvantages of wheel running include a much lower intensity of exercise, and variability among the amount of exercise that each animal receives. Voluntary wheel running has been shown to improve survival after ischemia (32), but future studies are needed to determine if voluntary running can protect the heart to the same extent as higher-intensity treadmill running.

A few studies have looked at the infarct sparing effects of swimming training. In these studies, animals were exposed to several hours of swimming per day for 7–8 wk, and infarctions were significantly reduced in swim-trained animals compared with sedentary counterparts (43, 141). The limitations of swimming protocols must also be acknowledged, as the exercise is often characterized by diving reflexes, animal stress from borderline drowning, and intermittent hypoxia (7, 42).

WHAT IS IT ABOUT EXERCISE THAT TRIGGERS A PROTECTIVE PHENOTYPE?

We are only beginning to understand what exercise does to “trigger” a preconditioning response. Exercise-induced activation of adenosine or opioid receptors, transient reactive oxygen species (ROS) production, AMP kinase, and/or surges in in-
Inflammatory cytokines are candidate triggers for the protection (a hypothetical schematic is presented in Fig. 1).

Several studies suggest that receptor-dependent signaling cascades are involved in triggering exercise cardioprotection. Adenosine receptor blockade abolished the cardioprotection evoked by intermittent bouts of tachycardia in paced dog hearts (39), suggesting that adenosine release at high heart rates initiates a cascade of events that confer resistance to infarction. The mechanism of action for adenosine receptor activation is surely multifactorial. Husain and Somani (54) recently found that the increase in myocardial antioxidant enzymes after acute exercise was abolished when exercise was performed in the presence of an adenosine receptor blocker. The authors did not investigate I/R injury, and more work is needed to determine if adenosine receptors initiate cardioprotective signaling following repetitive bouts of exercise. This is especially important in light of observations where chronic administration of adenosine loses efficacy to precondition the myocardium (127).

Opioids may also play a role in triggering exercise cardioprotection. A recent study found that blocking opioid receptors during the exercise treatment abolished the infarct salvage (35). Endogenous opioids can be released from a number of tissues (including heart) (34, 37), and administration of both opioid peptides and opioid receptor agonist preconditions tissue against injury (36, 45). Exercise may increase endogenous opioids in the coronary circulation via endocrine/autocrine pathways, although the exact role of endogenous opioids in exercise preconditioning warrants further investigation.

An attractive hypothesis is that the activation of adenosine and/or opioid receptors during exercise leads to protection via protein kinase C (PKC)-dependent mechanisms. Adenosine and opioid receptor signaling both converge on PKC (90, 130, 136), and the activation/translocation of PKC isoforms may induce a number of adaptive changes within the myocardium. The expression of several PKC isoforms is altered in the heart after repetitive exercise (23), and inhibiting PKC before exercise abolishes the infarct salvage (87, 134). Among the different PKC isoforms in the heart, several studies suggest a protective role for PKCε in particular (23, 87). It is not yet clear which cellular proteins “downstream” of PKC may be activated to mediate exercise preconditioning. PKC-dependent activation of heat shock protein 70 does not appear to be an absolute requirement for exercise cardioprotection (87), although PKC-dependent activation/trafficking of sarcolemmal ATP-sensitive potassium channel may be involved. Future research that elucidates downstream PKC targets will improve our understanding of its role in exercise cardioprotection.

Another putative trigger of exercise preconditioning is the transient release of ROS during exercise. Several studies have noted that the infarct-salvaging effects of exercise, as well as exercise-induced improvements in cardiac function, are abolished when antioxidants are given during the exercise (2, 96, 135). Exercise has been shown to increase the activity of myocardial NADPH oxidase, and inhibiting NADPH oxidase, a source of reactive oxygen species, abolished the protective effects of acute exercise (118). The notion that a small amount of ROS may lead to cardiac adaptations that confer resistance to infarction has been put forth in other preconditioning models (67), although the mechanisms that ultimately lead to decreased I/R damage are yet to be determined. A small ROS burst may increase antioxidant buffering capacity by promoting gene expression and protein synthesis, similar to the hormesis observed in skeletal muscle (58). ROS-dependent (redox) modulation of the ryanodine receptor after exercise

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**Fig. 1.** A putative sequence of events leading to exercise-induced protection against infarction. Postulated “triggers” of exercise-induced cardioprotection are denoted in green, with end-effectors labeled in red font. ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; sarcK_ATP, sarcolemmal ATP-sensitive K⁺ channel.
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was recently found to decrease sarcoplasmic reticulum (SR) calcium leak (118), although it is not clear if this mechanism is involved in delayed exercise cardioprotection [i.e., 24 h after exercise vs. acute effects investigated by Sanchez et al. (118)].

AMP-activated protein kinase (AMPK) is another candidate “trigger” for exercise preconditioning. AMPK is believed to be quiescent in the heart when energy supply-demand is in balance, but is activated during changing metabolic conditions (such as exercise or ischemia; reviewed in 4 and 66). Pharmacological activation of AMPK has been shown to reduce infarct size to a similar degree as exercise preconditioning (69). Cardiac AMPK is activated following treadmill running, with the AMPKα-2 isoform appearing to be the most responsive (30, 69, 95). Relating to the cardioprotective mechanism of action, AMPK activation is postulated to stimulate glucose/fat metabolism in the heart during metabolic stress (4, 66), and may promote translocation of cardiac ATP-sensitive potassium channel subunits (123; described in more detail below). The ischemic heart switches to anaerobic glycolysis very quickly, and both glycogen storage and sarcolemmal glucose transport are stimulated by AMPK. During reperfusion, AMPK is believed to augment fatty acid uptake and oxidation, further augmenting substrate flux through reenergized mitochondria. AMPK activation after exercise may protect the heart through better preservation of cardiac energetics, and there is both direct and indirect evidence that cellular ATP content is better maintained after I/R in exercised hearts (15, 56; addressed in more detail below). Inhibiting AMPK activation has not yet been shown to abolish exercise preconditioning. Using an AMPKα-2 dominant negative mouse model, Musi et al. (95) found that neither the ability of animals to exercise nor the maintenance of cardiac energy stores was altered with AMPKα-2 deficiency. Future experiments that directly examine exercise cardioprotection in AMPK knockout models, as well as development of more specific pharmacological tools that block AMPK activation, will improve our understanding of AMPK in exercise cardioprotection.

The role of cytokines on cardiac I/R injury in the literature is conflicting (31, 83). Regarding the involvement of cytokines in triggering exercise-induced cardioprotection, Yamashita et al. found that antibodies directed at both TNFα and IL1β abolished exercise protection when given prior to a single bout of exercise, and one-time administration of TNFα has been shown to reduce injury (135). Clearly more investigation is needed to clarify the role that cytokines play in exercise-induced cardioprotection, and whether cytokines such as TNFα appear to be involved in long-term exercise adaptations (such as cardioprotection or hypertrophy).

Among the candidate triggers and mediators involved in exercise-induced infarct sparing, augmented collateral coronary circulation, elevated nitric oxide synthase, heat shock proteins, and endoplasmic reticulum (ER) stress proteins do not appear to be obligatory for protection. For the interested reader, several excellent review articles have articulated these studies in more detail (111, 120).

IS EXERCISE-INDUCED CARDIOPROTECTION DUE TO IMPROVED ABILITY TO SCAVENGE ROS?

Superoxide dismutase. Exercise appears to improve at least some aspects of cellular ROS-scavenging systems. Superoxide production by complexes I and III of the electron transport chain, NADPH oxidase, xanthine oxidase, and NOS is believed to contribute to I/R injury in the heart (12). The “front line” of cellular superoxide detoxification involves enzyme-catalyzed dismutation by superoxide dismutase (SOD). Cellular compartmentation of SOD has led to several distinct isoforms including extracellular SOD, copper-zinc (Cu/Zn) SOD in the cytosolic compartment, and manganese (Mn) SOD in the mitochondrial matrix. Among these isoforms, increased MnSOD in particular has been found in many studies to correlate with protection against infarction.

In most exercise preconditioning studies, upregulated MnSOD has been observed following exercise. The duration (number of consecutive days) of exercise appears to be a key determinant to altering cardiac MnSOD levels. As noted in Table 1, most (but not all) investigations have observed increased MnSOD activity following short-term (1–5 days) exercise, but MnSOD mRNA (35) or protein (20) is not increased after acute exercise. In studies examining MnSOD with longer duration exercise protocols, there is a clear upregulation in both the activity (25, 52, 53, 62, 74, 109) and protein expression (18). This ability to augment MnSOD with exercise appears to be maintained in the aged heart (46, 62, 74). Supporting evidence for augmented MnSOD content and cardioprotection comes from mouse models where genetic overexpression of MnSOD protected against infarction (29), and genetic knockdown was associated with increased necrosis and impaired cardiac function (81).

Even within the same study, increased MnSOD activity can be observed without increased protein expression (135). Posttranslational modification of MnSOD is known to affect enzyme activity (133), and future experiments will help to determine if posttranslational modifications of MnSOD (such as dephosphorylation) are involved in the exercise-induced increase in MnSOD activity. As with exercise cardioprotection, upregulation in either the activity or protein content of MnSOD appear to be critically dependent on the intensity of exercise, as low-intensity treadmill running (27, 78, 109) and voluntary free wheel running (61) do not appear to increase myocardial MnSOD levels.

Pharmacological SOD mimetics show promise as a cardioprotective treatment across models of I/R (10, 26, 60, 65, 68). In recent human clinical trials, exogenous ROS scavengers decreased short-term injury (128), although there did not appear to be a long-term benefit. Further development of SOD mimetics, especially mitochondria-specific ROS scavengers (124), has potential in mitigating cardiac I/R injury.

Augmented H2O2 scavenging. Heightened SOD capacity appears to be involved in exercise cardioprotection, but there is little evidence of increased enzymes responsible for converting the SOD reaction product, H2O2, to water. In the myocardium, enzymatic detoxification of H2O2 depends on catalase, glutathione peroxidase, and thioredoxin. Only a few studies have noted increased catalase in the heart after exercise training (52), with most studies finding no difference in myocardial catalase activity after exercise (33, 44, 49, 61, 114, 115, 125). Most studies also find no change in glutathione peroxidase in the heart (33, 44, 49, 61, 114, 119, 125), consistent with observations where genetic overexpression of glutathione peroxidase did not confer protection against infarction (60). Finally, although there has not been as much investigation into...
cardiac thioreredoxin with exercise, it also appears to be uninfluenced by exercise (33). Taken together, heightened enzymatic scavenging of H₂O₂ does not seem to be a requisite for exercise-induced cardioprotection.

Glutathione and glutathione reductase. Exercise has been shown to increase total cardiac glutathione content (115), although this too appears to be intensity dependent as increased glutathione was not observed with life-long wheel running (61). It is not clear if glutathione reductase is involved in exercise cardioprotection, with some studies finding that glutathione reductase increases with exercise (62, 115) and others finding no change (25, 33, 61). Further work, especially those comparing glutathione content during/after oxidative stress, may provide more insight into glutathione and exercise cardioprotection.

ARE ATP-SENSITIVE POTASSIUM CHANNELS INVOLVED IN EXERCISE CARDIOPROTECTION?

A candidate protein complex that appears to be involved in exercise cardioprotection is the family of cardiac ATP-sensitive potassium (K<sub>K<sub>A<sub>TP</sub></sub>) channels. In the heart, there is one family of K<sub>K<sub>A<sub>TP</sub></sub> channels in the sarccolemmal membrane (sarcc<sub>K<sub>A<sub>TP</sub></sub>), and another in the mitochondrial inner membrane (mitoK<sub>K<sub>A<sub>TP</sub></sub> (55, 99). Sarcc<sub>K<sub>A<sub>TP</sub></sub> channels couple the metabolic status of the cell to the electrical excitability, and may be part of a negative-feedback mechanism utilized by cells to shorten the action potential and reduce excitability when energy supplies fall (see 101 for a review of K<sub>A<sub>TP</sub></sub> channels in cardiac preconditioning). K<sub>A<sub>TP</sub></sub>-dependent truncation of the action potential is believed to reduce cellular calcium levels by reducing L-type calcium transients. Functional cardiac sarcc<sub>K<sub>A<sub>TP</sub></sub> channels are believed to exist as hetero-octomers, with four pore-forming subunits and four accessory subunits inserted into the sarcclemma. Heart-specific isoforms were originally thought to consist of K<sub>4</sub>6.2 pore-forming subunits, and SUR2a accessory subunits, although recent findings indicate that the molecular identity of cardiac sarcc<sub>K<sub>A<sub>TP</sub></sub> may be more complicated and include multiple isoforms of both pore-forming (K<sub>ι</sub>) and accessory (SUR) subunits (140).

Several studies support a role for sarcc<sub>K<sub>A<sub>TP</sub></sub> channels in exercise preconditioning. Genetic knockout of sarcc<sub>K<sub>A<sub>TP</sub></sub> pore-forming subunits confers exercise intolerance (142), and upregulation of K<sub>A<sub>TP</sub></sub> channel subunits has been observed following both short-term and chronic exercise (17, 20). A confirmatory role for sarcc<sub>K<sub>A<sub>TP</sub></sub> channels in exercise-induced cardioprotection is provided in both short-term (28) and long-term (17) exercise studies where pharmacological block of sarcc<sub>K<sub>A<sub>TP</sub></sub> channels abolished the cardioprotection. In isolated cardiac myocytes exposed to I/R, Libonati et al. (79) showed that myocytes from trained animals had shorter action potentials than sedentary counterparts, consistent with the notion that exercise may protect the heart by augmenting the ability to repolarize. The issue of sarcc<sub>K<sub>A<sub>TP</sub></sub> channel subunit trafficking should be addressed in future exercise studies, as both PKC (41) and AMPK (123) have been shown to translocate sarcc<sub>K<sub>A<sub>TP</sub></sub> subunits to the sarcclemma and induce cardioprotection in other preconditioning models.

Sarcclemmal K<sub>A<sub>TP</sub></sub> channel opening during ischemia appears to be the crucial time point to protect tissue against infarction, as blocking the channels during reperfusion alone does not influence infarct size (59). During the ischemic period, there is probably a relatively short window for K<sub>A<sub>TP</sub></sub> channels to protect the heart. In rodent hearts exposed to ischemia, electrical activity in ventricular tissue continues for ~15 min, although mechanical function stops within in the first 2 min. Conduction velocity slows during ischemia due to the closure of gap junctions (“cellular uncoupling”) (24), and after approximately 15–20 min of ischemia cells become inexcitable due to rundown of sarcclemmal ion gradients and gradual sarcclemmal depolarization secondary to ATP depletion (see Fig. 2). This loss of electrical excitability is best observed in
global ischemia models (16), and is along the same timeline as the onset of ischemic contracture. Given the small window for sarcKATP-dependent protection, sarcKATP opening likely reduces infarction by delaying the onset of injury, although this delay may be inconsequential after prolonged ischemia (103). While speculative, this would explain why KATP channel block during longer ischemic bouts did not influence infarct size in sedentary male hearts (28, 59), as sedentary male rats are the most susceptible to injury and the window of protection from KATP channel opening may have passed during prolonged injury. Despite a higher propensity for injury in male animals (59), exercised male hearts still show increased sarcKATP channel expression (20), and blocking sarcKATP channels during ischemia abolishes the exercise preconditioning in both sexes (17, 28).

Although the opening of KATP channels reduces cellular injury, the consequence of increasing KATP currents may introduce electrical heterogeneity in the heart and promote arrhythmia, especially during reperfusion (reviewed in 22). Regarding the ischemic vs. reperfusion opening of KATP channels, it seems plausible that blocking sarcKATP channels during ischemia delays calcium overload and decreases infarction (59), while blocking sarcKATP channels during reperfusion has negligible effect on infarction but maintains cardiac function secondary to preservation of electrical stability (as observed in 57).

Unlike a number of other preconditioning models (reviewed in 100), blocking the mitochondrial KATP channel during I/R did not influence exercise-induced protection from infarction (17). Interestingly, administration of a mitoKATP blocker during exercise (vs. during I/R) does abolish the protection (38), indicating that mitoKATP activation might be involved in triggering the protective phenotype, but is not involved during the ischemic insult. It is important to note that the compound used as a “specific” blocker of mitoKATP (5-hydroxydecanoate) is notoriously nonspecific (17, 50–52). Future experiments using a better pharmacological approach, as well as improved insight into the molecular identity of mitoKATP, will advance our understanding regarding the involvement of mitoKATP in exercise preconditioning.

DOES PRIOR EXERCISE PROTECT AGAINST CELLULAR CALCIUM OVERLOAD?

Cellular calcium overload is central to the etiology of I/R damage (reviewed in 102). There is surprisingly little information regarding the effects of exercise on myocardial calcium handling during pathological circumstances. Jew and Moore (57) found no difference in cellular calcium content between sedentary and trained hearts exposed to I/R, although the method employed indicated only the total calcium content (and does not indicate if compartmentation of calcium, i.e., to the
mitochondria, occurred). Consistent with these findings, Libonati et al. (79) found no difference in cellular calcium transients in myocytes from sedentary and trained animals, although these measurements were done in myocytes isolated after experimental I/R. Bowles and Starnes (15) used radiolabeled calcium isopes and found that the exercise-trained heart appeared to be less susceptible to calcium overload after 30 min of reperfusion. One of the best physiological correlates to calcium overload is increased left ventricular diastolic pressure, and exercise does appear to protect the heart from diastolic dysfunction during I/R (18). Clearly much more investigation is warranted regarding the time-specific changes in cardiac calcium handling in hearts exposed to I/R to determine if prior exercise effectively delays the time course for calcium overload after the onset of ischemia.

WHAT IS THE ROLE OF CARDIAC MITOCHONDRIA IN EXERCISE PRECONDITIONING?

Exercise evokes adaptations in cardiac mitochondria that likely contribute to exercise-induced cardioprotection. While increases in Krebs cycle intermediates are not observed after exercise in the healthy heart, a number of exercise-induced changes in mitochondrial proteins associated with apoptosis and ROS scavenging have been observed (64). Interestingly, the subsarcolemmal population of mitochondria appeared to have more changes than the interfillibrar population of mitochondria (63). While there is much work to be done to understand how the altered mitochondrial proteome leads to infarct sparing, there are clearly phenotypic changes to mitochondria following exercise training. Isolated mitochondria from exercised animals are more resistant to apoptotic stimuli (64, 141). Whether or not delayed permeability transition pore opening (PTP) is a characteristic of mitochondria from exercised animals is equivocal, with some investigators finding no change in mitochondrial calcium tolerance (119) and others finding that mitochondria from exercised animals have a greater calcium retention capacity (64, 85). A likely explanation underlying differences between studies is the experimental methods employed. Starnes et al. (119) found no differences in calcium tolerance after administering one calcium pulse (200 nmol/mg mitochondrial protein) to deenergized mitochondria. Both Marcil et al. (85) and Kavazis et al. (64) found that PTP opening was delayed after training, but only when mitochondria were respiring on the complex II substrate succinate. Given the heightened ROS production with succinate-supported respiration, an improvement in endogenous ROS scavenging capacity is likely the culprit behind delayed PTP opening in these studies.

Taken together, mitochondria from exercised animals appear to be more resistant to injury, and it is likely that this healthier population of mitochondria is better able to preserve cellular energetics during oxidative stress. Preservation of energetics after exercise is reflected by a slower decline in myocardial ATP levels during I/R (14), maintenance of cardiac oxygen consumption after ischemia (15), prolonged time course for sarKATP channel opening during cellular anoxia (56), and resistance to apoptotic stimuli (64).

CONCLUSION

Exercise training is one of the few preconditioning stimuli that evokes sustainable protection against cardiac I/R injury. Improved oxidant buffering capacity, decreased cellular/mitochondrial calcium overload, and preservation of bioenergetics all appear to be involved in the underlying mechanisms. There is arguably no stimulus, whether pharmacological or physiological, that can promote such potent and long-lasting protection to hearts. Continued research into the mechanisms underlying exercise-induced cardioprotection, as well as novel pharmacological agents that are effective in exploiting these mechanisms, will improve our ability to treat those achy, breaky hearts.

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