Sex-specific and exercise-acquired cardioprotection is abolished by sarcolemmal K$_{\text{ATP}}$ channel blockade in the rat heart


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Submitted 28 November 2006; accepted in final form 15 January 2007


The present study was conducted to determine whether the infarct sparing effect of short-term exercise is dependent on the operation of the myocardial sarcolemmal ATP-sensitive K$^+$ (K$_{\text{ATP}}$) channel. Adult male and female Sprague-Dawley rats were exercised on a motorized treadmill for 5 days. Twenty-four hours following the training or sedentary period, hearts were isolated and exposed to 1 h of regional ischemia followed by 2 h of reperfusion on a modified Langendorf apparatus in the presence or absence of the sarcolemmal K$_{\text{ATP}}$ channel antagonist HMR-1098 (30 μM). Following the ischemia-reperfusion protocol, infarct size was determined as a percentage of the total ischemic zone at risk (ZAR). Short-term exercise reduced infarct size by 24% in males (32 ± 2% of ZAR; P < 0.01) and by 18% in females (26 ± 2% of ZAR; P < 0.05). Sarcolemmal K$_{\text{ATP}}$ channel blockade abolished the training-induced cardioprotection in both males and females, increasing infarct size to 43 ± 3% and 52 ± 4% of ZAR, respectively. In the absence of HMR-1098, infarct size was significantly lower in sedentary females than in males (33 ± 4% vs. 42 ± 2% of ZAR, respectively; P < 0.01). However, the presence of HMR-1098 abolished this sex difference, increasing infarct size by 58% in the sedentary females (P < 0.01) but having no effect on infarct size in sedentary males. This study demonstrates that the sex-specific and exercise-acquired resistance to myocardial ischemia-reperfusion injury is dependent on sarcolemmal K$_{\text{ATP}}$ activity during ischemia.

Ischemic heart disease is a leading cause of mortality in industrialized countries throughout the world. Myocardial infarction is often the initial manifestation of ischemic heart disease, and survival is inversely proportional to the size of the myocardial infarction sustained (13). A variety of preconditioning stimuli has proven to be effective at reducing myocardial infarct size when administered immediately before ischemia (e.g., ischemic preconditioning and adenosine receptor agonists), but the protective effect of these treatments is lost after repetitive administration (38, 53). Exercise training, however, has been consistently shown to confer sustainable protection against myocardial infarction in animal models (10, 26, 40, 56, 57) and has been associated with improved survival following an ischemic event in humans (27, 43). Despite substantial efforts to characterize the cardioprotective phenotype evoked by exercise training over the past decade, the precise mechanisms by which exercise reduces infarct size have not been fully elucidated.

The infarct-sparing effect of exercise has been reported following both long-term (>10 wk) (9, 10, 40) and short-term (1–5 days) training regimens (11, 26, 56). The majority of these studies have attributed the cardioprotection to an exercise-induced increase in manganese superoxide dismutase (MnSOD) protein in the heart and an associated resistance to myocardial oxidative stress during ischemia and reperfusion (10, 26, 57). However, a recent study by Brown et al. (11) indicated that 5 days of endurance exercise significantly reduced infarct size in both male and female rats without eliciting any significant increases in cardiac MnSOD levels, indicating that other cardioprotective mechanisms must be involved.

Myocardial ATP-sensitive K$^+$ (K$_{\text{ATP}}$) channels have been widely hypothesized to play an important role in the cardioprotection elicited by a variety of preconditioning stimuli (see Refs. 4 and 45 for review). K$_{\text{ATP}}$ channels are highly expressed in cardiomyocyte sarcolemma, where they are composed of four K$^+$ inwardly rectifying pore-forming subunits (Kir6.2) and four ATP-binding regulatory sulfonylurea receptor subunits (SUR2A). Sarcolemmal K$_{\text{ATP}}$ (sarcK$_{\text{ATP}}$) channels are believed to act as cytoprotective cellular energy sensors capable of preserving ionic homeostasis and cardiac bioenergetics during states of metabolic stress (1, 25). SarcK$_{\text{ATP}}$ channels are closed during states of metabolic surplus when cellular ATP levels are high and are open during times of metabolic challenge, resulting in K$^+$ efflux that shortens the cardiac action potential and limits intracellular Ca$^{2+}$ accumulation (44, 58). Channel gating is governed by the balance of local ADP and ATP concentrations, influenced by ATPase activity in the regulatory subunits integrated with intracellular metabolic pathways through phosphotransfer energetic signaling networks that modulate the nucleotide responsiveness and catalytic properties of the channel (1). Functional sarcK$_{\text{ATP}}$ channels are required for the cardioprotective benefits of pharmacological and ischemic preconditioning (25, 51, 52) and the physiological adaptations to acute and chronic exercise (32, 58). Recently, studies conducted by our laboratory found that short-term exercise enhanced the protein expression of sarcK$_{\text{ATP}}$ subunits in the male and female rat heart, which correlated with the training-induced infarct-sparing effect in both sexes (11). In another study, our laboratory demonstrated that pharmacological blockade of the sarcK$_{\text{ATP}}$
channel administered before ischemia abolished the infarct-sparing effect of chronic exercise training (>20 wk) in female rats (9). These studies have led to the hypothesis that sarK<sub>ATP</sub> channel activity may mediate the infarct-sparing effect conferred by various exercise training regimens. The present study was conducted to determine whether the infarct sparing effect of short-term exercise in male and female rats is abolished by HMR-1098, a selective myocardial sarK<sub>ATP</sub> channel antagonist.

**Methods**

Animal model and training protocol. Male and female Sprague-Dawley rats (5–8 mo old) were housed in a temperature-controlled facility maintained on a 12-h:12-h light-dark cycle with chow and water provided ad libitum. Animals were randomly assigned to an exercise training (Tr) or sedentary (Sed) group. Animals in the training groups were acclimated to the treadmill (14.5 m/min and 5–10 min/day) and handling procedures for 5 days before beginning the training protocol. Training consisted of 5 consecutive days of treadmill running at 15, 30, and 15 m/min for 10, 40, and 10 min at a 10% grade. All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Colorado at Boulder and are in compliance with guidelines established by the American Physiological Society.

**Ischemia-reperfusion protocol.** Twenty-four hours following the final training bout, animals were anesthetized with pentobarbital sodium (35 mg/kg), and hearts were rapidly excised for retrograde perfusion on a modified Langendorf heart perfusion apparatus. Adrenal and spleen weights and left tibia length were obtained at the time of death to assess systemic stress response and to provide an index of animal size, respectively. Hearts were perfused as previously described in detail by our laboratory (11) using an oxygenated Krebs bicarbonate buffer maintained at 37°C. A 3-Fr pressure-transducing catheter (Millar Instruments) was inserted into the left ventricle (LV) via the aortic valve for determination of LV pressures as previously described in detail by our laboratory (11) using an oxygenated Krebs bicarbonate buffer maintained at 37°C. A 3-Fr pressure-transducing catheter (Millar Instruments) was inserted into the left ventricle (LV) via the aortic valve for determination of LV pressures as previously described (10). After a 10-min equilibration period, baseline LV pressures and coronary flow rate were recorded, and hearts were perfused with buffer containing a specific sarK<sub>ATP</sub> channel antagonist (30 μM HMR-1098, a gift from Dr. Heinz Gögelein, Aventis Pharma) (SedHMR and TrHMR) or with buffer containing no drug (Sed and Tr). This concentration of HMR-1098 has been previously used in Langendorf-perfused heart preparations in our laboratory (9, 29) and others (12, 35) and effectively has abolished the cardioprotective effect of chronic exercise in female rats (9). Five minutes following initiation of HMR-1098 or control buffer, LV pressures and coronary flow were recorded a second time to examine the acute effects of HMR-1098, and hearts were exposed to ischemia induced by left coronary artery ligation using a reversible snare (10). Following the ischemic period, the snare was loosened and hearts were reperfused for 2 h. LV pressures and coronary flow were recorded at the end of the ischemic and reperfusion periods. Following the 3-h ischemia-reperfusion (I/R) protocol, hearts were prepared for determination of the ischemic zone at risk (ZAR) and infarct size using standard Evans blue and triphenyltetrazolium chloride staining methods previously described in detail by our laboratory (11). Infarct size and ZAR data are presented as a percentage of the ischemic ZAR.

**Statistical analyses.** All data are presented as means ± SE. Morphological data were compared by two (sex) by two (training status) analyses of variance (ANOVA) to determine differences due to sex or training status, with independent sample t-tests post hoc to examine individual group differences when appropriate. Infarct size and ZAR data were analyzed in male and female cohorts using two (drug) by two (training status) ANOVA to assess the main effects of training, HMR-1098, and any interaction between these factors. Coronary flow and LV pressure data were analyzed by repeated-measure ANOVAs. When appropriate, the simple effects of training (within sex) and sex (between Sed groups) on infarct size and hemodynamic variables were evaluated by independent sample t-tests. P < 0.05 was considered statistically significant.

**Results**

**Morphology data.** Morphological data are presented in Table 1. Male rats had significantly greater body weight and normalized LV and spleen weight compared with those in females. Adrenal gland weights normalized to tibia length were significantly greater in the females versus males and were not affected by exercise training in either sex. Training significantly reduced body weight in male but not female rats, which is consistent with previous evidence that male rats do not compensate for increased physical activity by increasing caloric intake (5, 49). Training had no effect on normalized LV or adrenal weights in either sex (ANOVA) but led to a significant reduction in spleen weight in males, indicating that the training protocol may have elicited some systemic distress in male rats (42, 50).

**Infarct size.** Mean infarct sizes and representative images from each group are presented in Fig. 1. No significant differences in the ischemic zone at risk for infarction (ZAR) existed among the experimental groups. A significant main effect of HMR-1098 and an interaction with training status were found in both males and females (ANOVA). Infarct size in the sedentary females (33 ± 4% of ZAR) was significantly lower than in the sedentary males (42 ± 2% of ZAR; P < 0.01). Short-term exercise reduced infarct size by 24% in males (32 ± 2% of ZAR; P < 0.01) and by 18% in the females (26 ± 2% of ZAR; P < 0.05). Administration of HMR-1098 during the I/R protocol abolished the training-induced reduction in infarct size in both males and females (to 43 ± 3% and 52 ± 44% of ZAR, respectively). Interestingly, HMR-1098 treatment also elicited a 58% increase in infarct size in the sedentary females (to 52 ± 4% of ZAR; P < 0.01) but had no effect on infarct size in the males (40 ± 1% of ZAR).

**Cardiac function.** Mean coronary flow and left ventricular developed pressure (LVDP) recordings at baseline, following 1 h of ischemia, and following 2 h of reperfusion are presented in Table 2. As expected, coronary flow and LVDP were significantly reduced by ischemia and reperfusion in both male and female hearts (P < 0.05). Following 1 h of regional ischemia, there were no significant differences in the effect of training or HMR-1098 on coronary flow in males or females. However, HMR-1098 significantly reduced flow in the SedHMR and TrHMR female hearts by the end of the 2-h

<table>
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<tr>
<th>Table 1. Animal morphological characteristics</th>
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<th>Male</th>
<th>Female</th>
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<tr>
<td></td>
<td>Sed</td>
<td>Tr</td>
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<tr>
<td>Body weight, g</td>
<td>327±6</td>
<td>310±3*</td>
</tr>
<tr>
<td>Left ventricle, mg</td>
<td>749±22</td>
<td>746±21</td>
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<tr>
<td>Left ventricle, mg/cm</td>
<td>21.6±0.6</td>
<td>21.2±0.4</td>
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<tr>
<td>Left adrenal, g/cm (×10&lt;sup&gt;6&lt;/sup&gt;)</td>
<td>6.8±0.2</td>
<td>7.3±0.3</td>
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<tr>
<td>Right adrenal, g/cm (×10&lt;sup&gt;6&lt;/sup&gt;)</td>
<td>7.4±0.9</td>
<td>7.1±0.4</td>
</tr>
<tr>
<td>Spleen, g/cm (×10&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>25.4±0.6</td>
<td>21.2±0.7*</td>
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Values are means ± SE. Sed, sedentary; Tr, trained. Tissue weights were normalized to tibia length to correct for variations in animal size. *P < 0.05 compared to Sed rats of the same sex.
reperfusion protocol compared with that in Sed and Tr hearts \( (P < 0.05) \). Coronary flow rate at the 2-h reperfusion time point correlated significantly with infarct size \( (r = 0.315; P = 0.015) \), suggesting that the HMR-1098-induced reduction in flow may be related to the level of necrotic tissue present in the LV by the conclusion of the reperfusion period. There was no statistically significant effect of HMR-1098 on LVDP following 2 h of reperfusion in males or females, which has been shown previously by our laboratory \((9)\) and others \((18)\).

**Acute effects of HMR-1098 exposure.** To examine the acute effect the HMR-1098 exposure on coronary flow rate and LVDP, recordings of each were obtained immediately before administering the drug (baseline) and 5 min after perfusion with HMR-1098 (Table 2). HMR-1098 had no acute effect on LVDP but elicited a significant reduction in coronary flow after 5 min of exposure in male and female hearts from trained and sedentary animals. These differences were no longer observed following the 1-h ischemic period.

![Figure 1](http://ajpheart.physiology.org/)  
*Fig. 1. Effect of exercise and HMR-1098 (HMR) on left ventricular (LV) infarct size in males and females. Infarct size is expressed as a percentage of the ischemic zone at risk (ZAR) as described in METHODS. Mean infarct sizes and representative LV images are illustrated for male (A) and female (B) rats exposed to the 5 day exercise protocol HMR-1098 or both treatments. *\( P < 0.05 \) vs. sedentary group (Sed); #\( P < 0.05 \) vs. training group (Tr) and Sed males and females.

**Table 2. Coronary flow and LV developed pressure during the perfusion protocol**

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<th>Male</th>
<th>Female</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>5 min preischemia</td>
</tr>
<tr>
<td></td>
<td>( \text{Coronary Flow, ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1} )</td>
<td>( % \text{change} )</td>
</tr>
<tr>
<td>Sed</td>
<td>22±1</td>
<td>22±1 ((-0.4))</td>
</tr>
<tr>
<td>Tr</td>
<td>23±1</td>
<td>23±1 ((-2.7))</td>
</tr>
<tr>
<td>SedHMR</td>
<td>20±1</td>
<td>16±1 ((-21.3)*)</td>
</tr>
<tr>
<td>TrHMR</td>
<td>21±1</td>
<td>17±1 ((-18.3)*)</td>
</tr>
<tr>
<td>Sed</td>
<td>21±1</td>
<td>21±1 ((+2.1))</td>
</tr>
<tr>
<td>Tr</td>
<td>20±1</td>
<td>19±1 ((-4.1))</td>
</tr>
<tr>
<td>SedHMR</td>
<td>23±1</td>
<td>18±1 ((-21.7)*)</td>
</tr>
<tr>
<td>TrHMR</td>
<td>22±1</td>
<td>16±0 ((-23.3)*)</td>
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Values are means ± SE. Coronary flow data are normalized to left ventricular (LV) mass in grams. The ischemia-reperfusion protocol significantly reduced coronary flow and LV developed pressure in hearts from trained (Tr) and sedentary (Sed) animals of both sexes \( (P < 0.01) \). HMR-1098 (HMR) administration for 5 min before ischemia acutely reduced coronary flow in both males and females regardless of training status. HMR-1098 also resulted in a significant decrease in flow in the female hearts following 2 h of reperfusion. \*\( P < 0.05 \), significantly different from Sed and Tr.
period but became evident in female hearts by the end of the 2 h reperfusion period.

**DISCUSSION**

The present study was conducted to determine whether the infarct-sparing effect of short-term exercise is dependent on myocardial sarcK<sub>ATP</sub> channel activity during I/R in male and female hearts. Selective blockade of the myocardial sarcK<sub>ATP</sub> channel completely abolished the infarct-sparing effect conferred by 5 days of exercise training in both male and female rats, indicating that an opening of the sarcK<sub>ATP</sub> channel is required for cardioprotection induced by short-term exercise training in both sexes. In addition, we have corroborated the findings of previous studies that have indicated that the female heart is intrinsically more resistant to myocardial infarction than the male heart (2, 11, 15, 41) and that this sex difference is abolished by sarcK<sub>ATP</sub> channel blockade (29).

**Effect of exercise and sarcK<sub>ATP</sub> blockade on infarct size.** The majority of studies that have investigated the benefits of exercise training on myocardial I/R injury have examined LV functional recovery and biochemical markers of tissue injury as primary end points following a variety of I/R protocols. The focus of the present study was on the ability of exercise to reduce myocardial infarct size, which has been recognized at the “gold standard” method for assessing the efficacy of preconditioning stimuli (45). It is important to note that the cellular mechanisms by which exercise training limits infarct size may be distinct from those responsible for limiting postischemic LV dysfunction (i.e., “stunning”) in the late phase of preconditioning (4). The present investigation is the first to examine the role of K<sub>ATP</sub> channel opening during I/R following short-term exercise. Evidence that sarcK<sub>ATP</sub> channel operation is required for the infarct-sparing effect of short-term exercise complements our previous findings that sarcK<sub>ATP</sub> activity is required for cardioprotection following long-term exercise and that both short- and long-term exercise increases sarcK<sub>ATP</sub> channel subunit expression in the heart (9, 11). Collectively, these studies strongly support a role for sarcK<sub>ATP</sub> channels in the infarct-sparing effect evoked by exercise training.

The cytoprotective mechanism(s) of myocardial K<sub>ATP</sub> channels in cardiac preconditioning have been the subject of intense study for over a decade (21, 45). It is hypothesized that K<sub>ATP</sub> channels act as cellular energy sensors capable of mediating a number of cytoprotective events that preserve cell integrity during states of metabolic stress (23, 34, 45). Early evidence for a protective role of K<sub>ATP</sub> channels came from Gross and Auchampach (20), who abolished the infarct-sparing effect of classic ischemic preconditioning with the K<sub>ATP</sub> channel blocker glibenclamide. Initially, a cardioprotective role was attributed to the sarcK<sub>ATP</sub> channel, but subsequent evidence led to the widely held notion that the mitochondrial K<sub>ATP</sub> (mitoK<sub>ATP</sub>) channel, the molecular identity of which remains unknown, is the chief mediator of cardioprotection (21, 23, 37). Indeed, administration of the putative mitoK<sub>ATP</sub> channel blocker 5-hydroxycanoate (5-HD) has been reported to block nearly all forms of preconditioning (45). However, recent studies with Kir6.2 knockout mice, which lack functional sarcK<sub>ATP</sub> channels, indicate that intact sarcK<sub>ATP</sub> channels are required for obtaining the cardioprotective benefits of ischemic preconditioning (25, 52) and the potassium channel opener diazoxide (51). Furthermore, recent work by our laboratory indicates that the infarct-sparing effect of long-term (>20 wk) exercise is maintained in the presence of mitoK<sub>ATP</sub> blockade during I/R (100 µM 5-HD) but is completely abolished by sarcK<sub>ATP</sub> blockade (30 µM HMR-1098) in the female rat heart (9). This finding is particularly significant because it indicates that exercise training represents the only known form of sustainable acquired cardioprotection that is not abolished by 5-HD.

Opening of sarcK<sub>ATP</sub> channels during ischemia has been hypothesized to provide cellular protection by evoking K<sup+</sup> efflux that shortens the myocardial action potential, leading to accelerated repolarization and limitation of intracellular Ca<sup2+</sup> loading (44, 58). However, preconditioning has been observed in the absence of action potential shortening (22), and Jovanovic et al. (30) found that cells transfected with cardiac sarcK<sub>ATP</sub> subunits confer resistance to simulated I/R in the absence of an action potential, suggesting that the channels may mediate their cytoprotective effects by other mechanisms. Reduced membrane excitability may contribute to the preservation of intracellular ATP levels stores during ischemia, which has been previously observed in exercise-trained hearts (6, 28). It has been proposed that an opening of the sarcK<sub>ATP</sub> channel may reduce tissue injury by sustaining cellular ATP levels and improving communication between the sarcolemma and mitochondria through phosphotransfer networks believed to be important for regulation of cellular homeostasis and survival during states of metabolic stress (1, 14). In addition to its role in preserving cellular bioenergetics and survival during ischemic stress, intact sarcK<sub>ATP</sub> channels, indicated by recent studies, are required for the general adaptive response to physiological stressors such as acute exercise and adrenergic stimulation (58) and for the attainment of the beneficial physiological adaptations to chronic exercise without cardiac injury (32). Furthermore, defective sarcK<sub>ATP</sub> channels, resulting from mutations of the ABC9 gene encoding the SUR2A regulatory subunit, predispose to dilated cardiomyopathy in humans (3). Taken together, these studies support an essential role of sarcK<sub>ATP</sub> channels in the adaptive cardiac response to acute and chronic stress relevant in health and disease (34).

**Sex-specific effect of sarcK<sub>ATP</sub> blockade.** Several studies have indicated that the female rat heart is intrinsically more resistant to I/R injury than the male heart (2, 11, 15, 29, 41). Interestingly, whereas HMR-1098 completely abolished the infarct-sparing effect of exercise in both males and females in the present study, it increased infarct size in the sedentary females by over 50%. Infarct size in hearts from sedentary male rats were unaffected by HMR-1098, which is consistent with results obtained by other investigators (18, 46). This sex-specific effect of HMR-1098 has been consistently observed in our laboratory (9, 29) and suggests that the female heart is intrinsically more dependent on myocardial sarcK<sub>ATP</sub> channel activity during ischemia than the male heart. This interpretation is congruent with a recent study by Gumina et al. (24) demonstrating a greater susceptibility to myocardial Ca<sup2+</sup> overload in vivo during dobutamine challenge and exaggerated postsischemic ventricular dysfunction in female sarcK<sub>ATP</sub>-deficient mice compared with their male counterparts. We have previously shown that the protein expression of sarcK<sub>ATP</sub> channel subunits is greater in the female compared with the male heart (11), which complements studies conducted by...
Ranki et al. (48) that have found female cardiomyocytes to express a greater pinacidil-induced outward K⁺ current and enhanced resistance to cellular Ca²⁺ overload compared with myocytes isolated from male hearts. In another study, Ranki et al. (47) demonstrated that 17β-estradiol increases sarKATP channel expression in H9c2 neonatal cardiac myotubes and provides sarKATP-dependent resistance to hypoxia-reoxygenation-induced cell injury (47), suggesting that estrogen may be at least partially responsible for the sex-specific effect. Interestingly, administration of 17β-estradiol protected against hypoxia-reoxygenation-induced Ca²⁺ loading in adult cardiomyocytes isolated from female guinea pigs, but not from males, through an estrogen receptor-dependent mechanism (31).

Effect of HMR-1098 on coronary flow. An administration of HMR-1098 significantly reduced coronary flow before ischemia in hearts from male and female rats in the present study, suggesting that the drug may be acting on sarKATP channels in vascular smooth muscle (VSM) to promote vasoconstriction under normoxic conditions (8). Recent evidence indicates that intact VSM KATP channels are required for metabolic-mediated vasodilation and cardiovascular tolerance to endotoxic shock (33). Whereas HMR-1098 has been shown to be highly selective to cardiac sarKATP channels compared with the pancreatic and vascular isoforms (17, 39), Liu et al. (36) demonstrated that 10–100 μM elicit a 10–50% inhibition of pinacidil-induced activity in channels expressing the Kir6.1/SUR2B subunit combination found in VSM (55). Moreover, other investigators have demonstrated a measurable effect of HMR-1098 on the coronary vasculature at micromolar concentrations. Administration of 1–10 μM HMR-1098 in isolated rat and guinea pig hearts induced slight, statistically insignificant decreases in coronary flow under normoxic conditions but significantly attenuated hypoxia-induced hyperemia at 10–100 μM (17, 18, 54). The results of the present study are similar to those reported by Gok et al. (19) where 30 μM HMR-1098 elicited a 20% increase in coronary perfusion pressure before ischemia in rat hearts perfused at a constant flow rate. Therefore, data from these studies and those presented herein suggest that 30 μM HMR-1098 may exert at least a mild effect on VSM KATP channel activity that results in a detectable reduction of coronary flow in the isolated perfused heart model.

The effect of HMR-1098 on coronary flow observed before ischemia in the present study was not observed after 1 h of regional ischemia in the male or female hearts but was evident following 2 h of reperfusion in only the female hearts. Whereas this effect may simply reflect the extensive LV necrosis that had manifested in the HMR-1098-treated female hearts by the end of the 3-h I/R protocol, it presents the intriguing possibility that the sex-specific effect of HMR-1098 on infarct size may involve a direct effect of the drug on postischemic coronary function. However, a recent study from our laboratory demonstrated that HMR-1098 had no effect on infarct size in females when administered exclusively during reperfusion, indicating that any contribution that the vascular effects of HMR-1098 may have on increasing infarct size must be due to effects sustained before or during the ischemic period (29). Determining the precise mechanism(s) and importance of any sex-specific effect of HMR-1098 on VSM KATP channels or coronary flow in the presence and absence of ischemia will require further investigation.

In summary, the present study indicates that the infarct-sparing effect of short-term exercise training is dependent on the opening myocardial sarKATP channels during I/R in male and female rats. Furthermore, the female rat heart is intrinsically more resistant to infarction than male hearts, and the cardioprotective female phenotype appears to involve an increased reliance on myocardial sarKATP channel opening during I/R. Evidence that sarKATP blockade increased infarct size in the sedentary females highlights the ongoing controversy over the safety of sulphonylurea drug use in patients with Type 2 diabetes and coronary artery disease (7, 16) and highlights the potential for increased cardiac risk in female patients, particularly in the setting of acute myocardial infarction. HMR-1098 had no appreciable effect on LV functional function during ischemia or reperfusion in males or females. However, a decrease in coronary flow was observed before ischemia in male and female hearts and, following I/R, in female hearts, suggesting that HMR-1098 may exert an effect on the coronary vasculature that may also exhibit sex-specific characteristics.

ACKNOWLEDGMENTS

We thank David A. Brown for useful insights throughout the course of this project.

GRANTS

This research was supported by the Howard Hughes Medical Institute (to R. T. Gardner and M. S. Johnson); a National Heart, Lung, and Blood Institute Grant HL-72790 (to R. L. Moore); and a postdoctoral fellowship from the American Heart Association (to A. J. Chicco).

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