Adrenal GRK2 lowering is an underlying mechanism for the beneficial sympathetic effects of exercise training in heart failure

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Submitted 28 July 2009; accepted in final form 19 March 2010

Adrenal GRK2 lowering is an underlying mechanism for the beneficial sympathetic effects of exercise training in heart failure. Am J Physiol Heart Circ Physiol 298: H2032–H2038, 2010. First published March 19, 2010; doi:10.1152/ajpheart.00702.2009.—Exercise training has been reported to exert beneficial effects on cardiac function and to reduce morbidity and mortality of chronic heart failure (HF). Augmented sympathetic nervous system (SNS) activity, leading to elevated circulating catecholamine (CA) levels, is a hallmark of chronic HF that significantly aggravates this disease. Exercise training has been shown to also reduce SNS overactivity in HF, but the underlying molecular mechanism(s) remain unidentified. We recently reported that adrenal G protein-coupled receptor kinase-2 (GRK2), an enzyme that regulates the sympathoinhibitory α2-adrenoceptors (α2-ARs) present in the CA-producing adrenal medulla, is upregulated in HF, contributing to the chronically elevated CA levels and SNS activity of the disease. In the present study, we tested whether exercise training can affect the adrenal GRK2-α2-AR-CA production system in the context of HF. For this purpose, a 10-wk-long exercise training regimen of adult male Sprague-Dawley rats starting at 4 wk postmyocardial infarction (post-MI) was employed, and examination at the end of this treatment period revealed significant amelioration of β-AR-stimulated contractility in response to exercise training, accompanied by cardiac GRK2 reduction and restoration of circulating plasma CA levels. Importantly, adrenal GRK2 expression (72 ± 5% reduction vs. post-MI untrained) and α2-AR number were also restored after exercise training in post-MI animals. These results suggest that exercise training restores the adrenal GRK2-α2-AR-CA production axis, and this might be part of the mechanism whereby this therapeutic modality normalizes sympathetic overdrive and impedes worsening of the failing heart.

sympathetic overactivity; adrenal G protein-coupled receptor kinase-2; catecholamines

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Exercise training on autonomic derangement and neurohumoral excitation in HF patients at rest have not been completely clarified (8).

Recently, we reported an important molecular mechanism in chronic HF that mediates the sympathetic overdrive of the failing heart (21). This mechanism involves the upregulation of GRK2 in the CA-producing adrenal medulla of HF animals, which leads to increased downregulation and G protein uncoupling of the α2-ARs present in the chromaffin cell membranes of the adrenal gland that normally exert negative feedback control on CA turnover (21). Thus these receptors become severely dysfunctional in HF, which results in chronically elevated CA secretion and circulating levels in HF (21). In the present study, we sought to investigate whether exercise training could favorably affect this deregulated adrenal GRK2-α2-AR-CA production axis in HF and whether this could represent a molecular neurohormonal mechanism by which exercise training curbs the sympathetic overactivity of chronic HF. We found, in an experimental rat model of chronic HF induced by MI, that this is indeed the case. Therefore, adrenal GRK2 lowering appears to be an important molecular mechanism for the sympathoinhibitory effects of exercise training in HF.

MATERIALS AND METHODS

The study protocol was designed in accordance with the “Guide for the Care and Use of Laboratory Animals” of the National Institutes of Health [DHEW Publication No. (NIH) 85-23, Revised 1996, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205] and was approved by the Ethics Committee for the Use of Animals in Research of our institution.

Experimental groups. Fifty-five Sprague-Dawley male rats (~300 g; Charles River Laboratories, Calco, Italy) entered the study and were randomly assigned to one of the three experimental groups. Sham-operated and post-MI rats were housed sedentary for 14 wk (sham, n = 11; post-MI/untrained, n = 22); one group of post-MI HF rats was assigned to a 4-wk sedentary period followed by 10 wk of treadmill exercise protocol (post-MI/trained, n = 22).

Experimental procedures. MI was induced by surgical ligation of the proximal tract of the left anterior descending coronary artery, as previously described (17). The overall mortality rate (early plus late mortality) for this procedure was ~45%, as previously reported (17). Serial M-mode echocardiographic evaluations were performed at 4 wk after surgery and at the end of the study protocols in anesthetized (2% isoflurane) rats, using the VisualSONICS VeVo 770 imaging system with a 716 scan head, as described previously (30). At the end of the study protocol, all animals underwent in vivo cardiac hemodynamic evaluation. Rats were anesthetized with 2% isoflurane, and venous access was obtained via the right external jugular vein. A 2-0 French micromanometer was placed into the left ventricle (LV) through the left carotid artery. Data were acquired at baseline and after maximal infusion of isoproterenol, as previously reported (30). The LV pressure data were then analyzed on a PowerLab system (Colorado Springs, CO) with custom software to derive the maximal and minimal first derivative of the pressure rise (dP/dt) and LV −dP/dt, respectively, as well as heart rate.

Exercise training protocol. At 4 wk after MI, rats assigned to the post-MI/trained group underwent a training aerobic program consisting of a 10-wk treadmill protocol. In the first 2 wk, exercise relative intensity was set at 40–50% of maximal oxygen uptake (VO2max), whereas in the following 8 wk, rats exercised 5 days/wk, 45 min/day, with a running speed of 17 m/min (15° inclination) and an exercise relative intensity calculated at 75–80% of VO2max, as previously reported (17). Exercise tolerance was evaluated immediately before and after exercise training or sedentary period, as previously reported (17).

RNA isolation and real-time RT-PCR. Cardiac total RNA isolations, reverse transcription to cDNA, and quantitative real-time RT-PCR were carried out as previously described (30). The oligonucleotide primers used to examine expression of genes were as follows: transforming growth factor-β1 (TGF-β1: forward primer, 5'-GGCACAGGTTTGAGGCCCTTCCA-3'; reverse primer, 5'-CAGGTTGTGACCCCTTTCCA-3'), collagen type I (Col-I: forward primer, 5'-CCAGTTGCAGTATGGAAAGCA-3'; reverse primer, 5'-AGGTTGATTCGTCGG-3'), and atrial natriuretic factor (ANF: forward primer, 5'-TGCCGGTGAAGAGTGAGTC-3'; reverse primer, 5'-TGGCTTTCAAGAGGACAGAT-3'). For normalization, 18S rRNA was used (forward primer, 5'-TCAGAAAGGAAGTCCGGAGG-3'; reverse primer, 5'-GCATCTCA-AGGGCATCAC-3'). PCR conditions were 95°C for 3 min and 40 cycles of 95°C for 10 s and 62.5°C for 45 s. Specificity of PCR products was confirmed by gel electrophoresis.

Plasma CA secretion measurements. Plasma epinephrine (Epi) and norepinephrine (NEpi) levels were determined by enzyme-linked immunosorbent assay, performed on rat plasma samples using the BI-CAT EIA kit from ALPCO Diagnostics (Windham, NH), as described previously (21, 22).

Western blotting. Western blots to assess protein levels of GRK2 (sc-562; Santa Cruz Biotechnology, Santa Cruz, CA) were performed using protein extracts from excised and homogenized hearts and adrenal glands, as described previously (30).

Saturation ligand-binding. Plasma membranes from excised adrenal glands were prepared as described previously (21), and saturation binding was performed using α2-AR radioligands ([3H]rauwolscine), as reported previously (21). Data were analyzed by nonlinear regression analysis using GraphPad Prism (GraphPad Software).

Measurement of infarct size. Infarct size was examined in all experimental groups at the end of the study period. Briefly, hearts were frozen in liquid nitrogen and sectioned from apex to base into 2-mm slices. To delineate the infarct size, sections were incubated in 1% (wt/vol) triphenyltetrazolium chloride (Sigma) in PBS (pH 7.4) at room temperature for 15 min. For each section, the infarct size of the LV was calculated from enlarged digital photos using SigmaScan 5.0 software, as described previously (30).

Statistics. Data were analyzed using one-way ANOVA, followed by Bonferroni’s post hoc analysis or unpaired t-test, as appropriate. Significance was set at a level of P < 0.05, and all data are means ± SE.

RESULTS

Effects of exercise training on cardiac function and dimensions. Adult male Sprague-Dawley rats underwent MI to induce chronic HF or a sham operation. At 4 wk post-MI, rats were randomized to a training or sedentary protocol. Echocardiography at this time point revealed equal levels of cardiac dysfunction between the two randomized post-MI groups (data not shown). As shown in Fig. 1, 10 wk of exercise training failed to improve ejection fraction (EF) compared with the untrained post-MI animals. As expected, EF was severely reduced in both HF groups compared with the sham group. However, training induced a reduction in LV diastolic diameter in trained compared with untrained rats (Fig. 1 and Table 1). In addition, training increased exercise tolerance, reduced body weight (BW), and significantly increased LV weight (LVW) and LVW-to-BW ratio compared with the sedentary post-MI (untrained) group. These results indicate that exercise is capable of limiting LV dilation of the post-MI failing heart. Infarct size was not affected by exercise (Table 1), probably because most of the LV remodeling and infarct establishment occurs within the first week after MI.

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Effects of exercise training on adrenergic-stimulated cardiac contractility. Basal LV +dP/dt maximal and −dP/dt minimal values did not differ between the experimental post-MI groups, although they were significantly reduced compared with the sham animals, as expected (Fig. 2 and Table 1). Consistent with the echocardiographic data described above, this result indicates that training is not able to increase resting LV performance. However, trained rat hearts displayed significantly improved LV contractile responses to β-AR stimulation by isoproterenol in contrast with the untrained rat hearts, whose β-AR stimulated contractile responses were markedly impaired (Fig. 2). The responses of sham rat hearts to isoproterenol stimulation were far better than those of both post-MI groups, as expected. This finding is entirely consistent with the exercise-induced increase in cardiac functional β-AR density observed in post-MI/trained hearts compared with post-MI/untrained (Supplemental Fig. 1). (Supplemental data for this article is available online at the American Journal of Physiology-Heart and Circulatory Physiology website.) Thus exercise training seems to enhance the responsiveness of the failing heart to β-AR procontractile stimulation.

Effects of exercise training on cardiac remodeling gene profile. We next investigated the gene expression patterns of post-MI cardiac remodeling in our experimental groups. As expected, LV ANF mRNA expression, typically associated with cardiac hypertrophy, was significantly increased in the untrained post-MI group compared with sham at 14 wk after MI (Fig. 3); however, exercise training significantly reduced cardiac ANF expression in HF (Fig. 3). We also examined cardiac mRNA levels of TGF-β1 and Col-1 mRNA as molecular markers of remodeling/fibrosis. Both were significantly elevated in the untrained post-MI group compared with sham but were markedly reduced in the exercise-trained post-MI group (Fig. 3). These results clearly demonstrate, also at the molecular level, the positive effects of exercise training on cardiac adverse remodeling.

Effects of exercise training on plasma CAs in HF. As shown in Fig. 4, 10 wk of exercise training resulted in a marked reduction of circulating plasma levels of both NEpi and Epi compared with the post-MI untrained group. In fact, levels in the trained group were similar to those in the sham group, suggesting a complete restoration of circulating CA levels in HF by exercise training.

Adrenal and cardiac GRK2 levels in HF after exercise training. The finding that exercise training normalizes circulating CA levels in chronic HF rats prompted us to investigate its effects on adrenal GRK2 expression levels, since the latter was recently shown to be a critical regulator of adrenal CA production and of circulating CA levels in health (22) and in chronic HF (21, 23). As shown in Fig. 5, untrained post-MI rats display marked adrenal GRK2 upregulation at the protein level compared with sham-operated animals, consistent with our previous findings in a rat model of chronic post-MI HF (21). Importantly, exercise training resulted in restoration of adrenal GRK2 protein levels in these HF rats (Fig. 5), which is entirely consistent with reduced adrenal CA production and the observed normalization of plasma CA levels in these animals (Fig. 4).

In addition, we examined cardiac GRK2 levels after exercise training in our HF animals, and we found, consistent with previous reports by our group (17, 18), that exercise training reverses the pathogenic upregulation of cardiac GRK2 normally present in chronic HF, as well (Supplemental Fig. 2).

Adrenal α2-AR density in HF after exercise training. To provide additional confirmatory evidence that normalization of adrenal GRK2 levels is indeed mechanistically involved in the reduction of sympathetic overactivity and plasma CA levels by exercise training in HF, we also measured total adrenal α2-AR
Table 1. Physical, hemodynamic, and echocardiographic data in sham-operated and post-MI HF rats at 10 wk sedentary or exercise protocols

<table>
<thead>
<tr>
<th>Exercise tolerance (min)</th>
<th>Sham Operated</th>
<th>Post-MI/Untrained</th>
<th>Post-MI/Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before protocols</td>
<td>26 ± 4</td>
<td>11 ± 3*</td>
<td>10 ± 2*</td>
</tr>
<tr>
<td>After protocols</td>
<td>25 ± 3</td>
<td>9 ± 2*</td>
<td>18 ± 3†</td>
</tr>
<tr>
<td>Physical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW, kg</td>
<td>0.478 ± 0.028</td>
<td>0.453 ± 0.022</td>
<td>0.402 ± 0.020†</td>
</tr>
<tr>
<td>HW, g</td>
<td>1.22 ± 0.2</td>
<td>2.39 ± 0.4*</td>
<td>2.68 ± 0.5†</td>
</tr>
<tr>
<td>HW/BW, g/kg</td>
<td>2.55 ± 0.19</td>
<td>5.28 ± 0.27*</td>
<td>6.67 ± 0.40†</td>
</tr>
<tr>
<td>Lung wt, g</td>
<td>1.65 ± 0.35</td>
<td>3.54 ± 0.66*</td>
<td>2.60 ± 0.32†</td>
</tr>
<tr>
<td>Lung wt/BW, g/kg</td>
<td>3.96 ± 0.65</td>
<td>8.81 ± 0.89*</td>
<td>6.74 ± 0.91†</td>
</tr>
<tr>
<td>LV catheterization, basal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>353 ± 12</td>
<td>345 ± 11</td>
<td>332 ± 10</td>
</tr>
<tr>
<td>LV +dP/dt, mmHg/s</td>
<td>6914 ± 532</td>
<td>4222 ± 326*</td>
<td>4523 ± 410*</td>
</tr>
<tr>
<td>LV –dP/dt, mmHg/s</td>
<td>–7012 ± 498</td>
<td>–3869 ± 347*</td>
<td>–3984 ± 406*</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>127 ± 9</td>
<td>104 ± 6*</td>
<td>110 ± 9*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>3.35 ± 0.9</td>
<td>23.7 ± 3.1*</td>
<td>17.9 ± 2.3†</td>
</tr>
<tr>
<td>LV catheterization, isoproterenol (333 ng/kg BW)</td>
<td>415 ± 19</td>
<td>409 ± 13</td>
<td>401 ± 15</td>
</tr>
<tr>
<td>LV +dP/dt, mmHg/s</td>
<td>15978 ± 980</td>
<td>6968 ± 645*</td>
<td>9534 ± 584†</td>
</tr>
<tr>
<td>LV –dP/dt, mmHg/s</td>
<td>–8905 ± 334</td>
<td>–4973 ± 321*</td>
<td>–6222 ± 389†</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LV EF, %</td>
<td>65.4 ± 0.6</td>
<td>30.7 ± 1.8*</td>
<td>33.6 ± 1.4*</td>
</tr>
<tr>
<td>LVIDd, mm</td>
<td>8.48 ± 0.12</td>
<td>10.50 ± 0.20*</td>
<td>9.39 ± 0.22†</td>
</tr>
<tr>
<td>LVSwd, mm</td>
<td>5.36 ± 0.08</td>
<td>8.92 ± 0.27*</td>
<td>7.81 ± 0.21†</td>
</tr>
<tr>
<td>LVAWd, mm</td>
<td>1.51 ± 0.07</td>
<td>1.09 ± 0.05*</td>
<td>1.06 ± 0.06*</td>
</tr>
<tr>
<td>LVADWs, mm</td>
<td>2.68 ± 0.31</td>
<td>1.10 ± 0.04*</td>
<td>1.08 ± 0.06*</td>
</tr>
<tr>
<td>LVDPd, mm</td>
<td>1.48 ± 0.05</td>
<td>1.99 ± 0.09*</td>
<td>2.38 ± 0.17†</td>
</tr>
<tr>
<td>LVDPWs, mm</td>
<td>2.40 ± 0.31</td>
<td>2.38 ± 0.37</td>
<td>2.79 ± 0.45</td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>42.3 ± 4.3</td>
<td></td>
<td>43.8 ± 4.9</td>
</tr>
</tbody>
</table>

Data are means ± SE in sham, postmyocardial infarction (post-MI)/untrained, and post-MI/trained heart failure (HF) rats. *P < 0.05 vs. sham. †P < 0.05 vs. post-MI/untrained. One-way ANOVA analysis and Bonferroni’s test were used among all 3 groups. BW, body weight; HW, heart weight; HR, heart rate; EF, ejection fraction; LV, left ventricular; dP/dt, rate of rise in pressure; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; LVIDd, LV internal diameter at diastole; LVIDs, LV internal diameter at systole; LVADWd, LV anterior wall diameter at diastole; LVADWs, LV anterior wall diameter at systole; LVDPd, LV posterior wall diameter at diastole; LVDPWs, LV posterior wall diameter at systole.

plasma membrane density in our three experimental groups of animals. As shown in Fig. 6, untrained post-MI rats display a significant adrenal α2-AR downregulation compared with control healthy sham animals, consistent with our previous report (21). Exercise training of post-MI rats, however, restores adrenal α2-AR density to the control sham group value (Fig. 6), thus providing additional support to the notion that exercise training normalizes circulating CA levels in HF by restoring the adrenal GRK2-α2-AR-CA production system.

**DISCUSSION**

In the present study, we have reported a novel molecular neurohormonal mechanism for the beneficial effects of exercise training on counterbalancing sympathetic overactivation and the enhanced circulating CA levels of chronic HF that significantly increase the morbidity and mortality of this devastating disease (8, 23). This mechanism involves lowering and restoration of adrenal GRK2 levels/activity, which results in marked reduction of adrenal CA production and secretion via decreased adrenal α2-AR desensitization/downregulation. As a result, circulating CA levels are normalized.

This finding is of particular importance because several studies over the past couple of decades have reported that exercise training counteracts the neurohormonal and, in particular, the catecholaminergic activation of chronic HF in humans and in several animal models of the disease (8, 21, 23, 30); however, essentially no evidence has been provided as to the molecular mechanisms mediating this beneficial effect of this therapeutic modality in HF (8).

Circulating CAs originate from the adrenal medulla in the form of Epi (mainly) and NEpi, which are secreted at a ratio of ~80 to 20%, respectively, under normal conditions (23).
Spilled-over NEpi produced at sympathetic nerve endings also contributes to the total circulating amount of CAs. Adrenal CA production is under tight regulation by sympathoinhibitory 2-ARs, which are expressed in the adrenal medulla and inhibit CA release (23). 2-AR function in turn is regulated by GRK2, which phosphorylates and desensitizes the 2-AR, thus suppressing its function (30, 35). By reducing GRK2 activity on adrenal 2-ARs, exercise training appears to restore 2-AR number and CA feedback inhibition, and this represents a mechanism whereby it reduces circulating CA levels in chronic HF.

Moreover, GRK2-dependent 2-AR dysfunction could be responsible for the poor sympathoinhibitory efficacy of the 2-AR agonist moxonidine in heart failure. In fact, the MOXSE and MOXCON trials (33, 34), two recent clinical trials of moxonidine for the treatment of HF, were discontinued because of excess mortality in the treatment group (7, 34). A possible reason for the failure of these trials could have been the dysfunction of peripheral 2-ARs. Thus cardiac sympathetic nerve terminals and the adrenal glands might not adequately respond to 2-AR agonists because of the impaired 2-AR function. In this regard, the present study suggests that exercise training is able to restore 2-AR function in HF, and this might result not only in the observed reduction of circulating catecholamine levels but also, perhaps, in a potential increased efficacy of moxonidine in HF treatment.

Of note, these favorable molecular/physiological alterations in the adrenal gland post-MI are coupled with beneficial changes in β-AR stimulated performance. More specifically, although basal function seems to be unaffected by exercise training, as indicated by EF and basal dP/dt responses, LV diastolic diameters and isoproterenol-stimulated contractility are significantly improved. These findings are in complete accordance with previous reports indicating that exercise training affects only slightly (if at all) EF but increases β-AR-dependent contractility of the failing heart (17, 18).

In addition, improvement in cardiac parameters by exercise training also includes a significant downregulation of cardiac GRK2. This kinase is normally upregulated in the failing heart and contributes significantly to the impairment of cardiac β-AR responsiveness, since it desensitizes and downregulates α2-AR agonist moxonidine in heart failure.
In conclusion, the present study provides the first report of a molecular mechanism for the well-documented beneficial effects of exercise training on curbing the cardiotoxic sympathethic overactivation of chronic HF. Our data indicate that exercise training can exert a similar (and/or complementary) neurohormonal action to that of β-blockers in combating the autonomic derangements that confound and aggravate chronic HF. In addition, the present study further reinforces the therapeutic value of exercise training in the treatment of cardiovascular disease. Finally, enhanced adrenal GRK2, as we have previously shown, is confirmed as an important pathogenic mechanism for the sympathetic overdrive in HF, and thus its lowering/inhibition represents a novel sympatholytic strategy for HF therapy.

Fig. 5. G protein-coupled receptor kinase-2 (GRK2) expression in adrenal homogenates purified from all 3 experimental groups at the end of the study period. Top: representative Western blots. Bottom: average densitometric quantitative analysis from blots showing the ratio of GRK2 to GAPDH. Data are means ± SE (n = 8 for each group). *P < 0.05 vs. sham or post-MI/trained groups. ANOVA analysis and Bonferroni’s test were used among all groups.

Fig. 6. Total α2-adrenoceptors (α2-AR) density in plasma membranes purified from the adrenal glands of all 3 experimental groups at the end of the study period. Data are means ± SE (n = 5 for each group). *P < 0.05 vs. sham or post-MI/trained groups. ANOVA analysis and Bonferroni’s test were used among all groups.

The favorable effects of exercise training on adverse remodeling of the failing myocardium are also evident by the restoration of the expression of various remodeling-associated genes such as ANF, TGF-β1, and Col-1 in our trained post-MI experimental group. The observation that despite a complete restoration of the expression of these genes, EF was left unaffected and LV dimensions also were not completely restored by exercise training probably is due to the fact that our exercise training regimen started at 4 wk post-MI, a time point by which the pathological restructuring/remodeling of the failing heart is already established. However, even in the absence of a favorable effect of exercise on resting LV function in failing hearts, significant improvement of cardiac inotropic reserve is present. Furthermore, the reduction of LV end-diastolic pressure and lung congestion indicate an overall improvement induced by exercise in cardiac and systemic hemodynamics (Table 1). Another important finding was the exercise-induced increase of cardiac β-AR density, which is completely consistent with the enhanced cardiac adrenergic responses to isoproterenol (Supplemental Fig. 2).

Our results confirm previous evidence showing that low to moderate treadmill exercise, started late after a large MI, offers beneficial effect on the failing heart (17, 20, 25, 38). In contrast, training programs using higher exercise intensity and started early after MI have reported detrimental effects on LV geometry and survival in rats (9, 15). In particular, the use of endurance swimming, which is associated with higher mental and hemodynamic stresses compared with treadmill exercise, and a longer daily/weekly exercise time strongly differentiate these previous training strategies from that used in the present investigation and may account for the negative effects of exercise in post-MI animals observed by these investigators (9, 15).

With regard to the effect of exercise on survival of HF patients, only meta-analysis studies that reported a favorable effect of training at reducing long-term mortality are available to date (13, 28, 37). Recently, the largest controlled trial of exercise training in HF, the ACTION trial (24), has shown a statistically significant, albeit modest, effect for the primary end points of all-cause mortality or all-cause hospitalization and for the secondary end points of cardiovascular mortality or HF hospitalization. However, no definitive conclusions have been made so far on this controversial issue. Thus further studies are needed to clarify the therapeutic effect of exercise in reducing cardiovascular death and improving quality of life of HF patients.

The β-ARs within the failing cardiac myocytes (2, 35, 36). Indeed, we observed a marked upregulation of GRK2 in hearts of untrained post-MI rats, and the exercise training-induced normalization of cardiac GRK2 levels represents further additional molecular evidence for cardiac improvement by this HF treatment. These findings are in line with previous observations by our group in the failing myocardium (17) and in the aged heart (18) and by others in hypertensive animals (19).
ADRENAL GRK2 NORMALIZATION BY EXERCISE TRAINING

REFERENCES

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


