Moderate intensity of regular exercise improves cardiac SR Ca$^{2+}$ uptake activity in ovariectomized rats

Tepmanas Bupha-Intr, Jitanan Laosiripisan, and Jonggonnee Wattanapermpool

Department of Physiology, Faculty of Science, Mahidol University, Bangkok, Thailand

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Bupha-Intr T, Laosiripisan J, Wattanapermpool J. Moderate intensity of regular exercise improves cardiac SR Ca$^{2+}$ uptake activity in ovariectomized rats. J Appl Physiol 107: 1105–1112, 2009. First published August 13, 2009; doi:10.1152/japplphysiol.00407.2009.—The impact of regular exercise in protecting cardiac deteriorating results of female sex hormone deprivation was evaluated by measuring changes in intracellular Ca$^{2+}$ removal activity of sarcoplasmic reticulum (SR) in ovariectomized rats following 9-wk treadmill running exercise at moderate intensity. Despite induction of cardiac hypertrophy in exercised groups of both sham-operated and ovariectomized rats, exercise training had no effect on SR Ca$^{2+}$ uptake and SR Ca$^{2+}$-ATPase (SERCA) in hormone intact rat heart. However, exercise training normalized the suppressed maximum SR Ca$^{2+}$ uptake and SERCA activity in ovariectomized rat heart. While exercise training normalized the leftward shift in pCa ($-\log[\text{Ca}^{2+}]$)-SR Ca$^{2+}$ uptake relation in ovariectomized rats, no effect was detected in exercised sham-operated rats. Similar phenomena were also observed on SERCA and on phospholamban (PLB) phosphorylation levels; exercise training in ovariectomized rats enhanced SERCA expression to reach the level as that in sham-operated rats, in which there were no differences in SERCA and phospho-PLB levels between sedentary and exercised groups. In addition, the reduction in phospho-Thr$^{17}$ PLB in myocardium of ovariectomized rats was abolished by exercise training. These results showed that regular exercise maintains the molecular activation of cardiac SR Ca$^{2+}$ uptake under normal physiological conditions and is able to induce a protective impact on cardiac SR Ca$^{2+}$ uptake in ovarian sex hormone-deprived status.

training in preventing changes in cardiac myofilament Ca$^{2+}$ activation induced by ovariectomy, and knowledge of the mechanisms underlying this protective activity will provide supportive information for promoting exercise therapy to help lower the risk associated with hormone replacement therapy.

Evidence has demonstrated possible interactive effects between exercise training and female sex hormones on cardiac performance (5, 6, 11, 23). As a result, exercise training in females exerts less benefit on cardiac function until meno-pause. Exercise training in rats significantly reduced myocardial infarct size following ischemia-reperfusion injury better in males than in females (5). In genetically hypertensive rats, exercise training reduced blood pressure only in males but not in females (11). These sex-dependent responses in cardiac performance to exercise training raise the possibility that exercise-induced cardiac adaptation may provide a similar beneficial effect as that of female sex hormones. In swimming exercise, a significant increase in the expression of myosin V1 isoenzyme was clearly observed in the heart of male and ovariectomized rats but not in intact females (23). Introducing moderate intensity of treadmill running in female rats, cardiac hypertrophy was induced without changes in myofilament Ca$^{2+}$ response and myosin heavy chain (MHC) expression compared with sedentary controls (6). However, under ovarian sex hormone-deprived condition, the same running program induced increases of both maximum myofilibrillar ATPase activity and α-MHC expression, but induced a decrease in myofilament Ca$^{2+}$ sensitivity in the heart of the hormone intact rat. This apparent exercise-induced cardioprotection following deprivation of female sex hormones suggests common mechanistic signals of exercise and female sex hormones on cardiac contractile activation.

Two major stress signals, sympathetic outflow and heat production, which are certainly induced during exercise, result in altered expression of cardiac β$_1$-adrenoceptors and heat shock protein 70, which appear to play, in part, a mechanistic role in the cardioprotective effects (6). Altered β$_1$-adrenoceptors induce downstream Ca$^{2+}$ modifications of many sites from plasma membrane Ca$^{2+}$ influx to SR Ca$^{2+}$ handling. Following ovariectomy, isolated ventricular myocytes demonstrated depressed shortening, with prolonged relaxation in association with a decreased peak with prolonged decay of Ca$^{2+}$ transients (8, 28). There is also a depression in Ca$^{2+}$ uptake and Ca$^{2+}$-ATPase activity of cardiac SR vesicles prepared from 10 wk ovariectomized rat heart compared with sham-operated control, which appeared to be associated with a downregulation of SR Ca$^{2+}$-ATPase (SERCA) (7). These changes in the SR Ca$^{2+}$ movement are in good agreement with an upregulation of cardiac β$_1$-adrenoceptors detected after ovariectomy. Inasmuch as exercise training inhibits receptor upregulation in ovariectomized rat heart (6), it suggests a potential mechanistic

Address for reprint requests and other correspondence: J. Wattanapermpool, Dept. of Physiology, Faculty of Science, Mahidol Univ., Rama 6 Road, Bangkok 10400, Thailand (e-mail: tejwt@mahidol.ac.th).

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THE FRAMINGHAM HEART STUDY of the United States National Heart, Lung, and Blood Institute has indicated a benefit of female sex hormones on cardiovascular function (31). Postmenopausal women with hormone replacement therapy demonstrate a better cardiac performance than those without hormone supplement (1, 27). However, it was recently reported by the Women’s Health Initiative (WHI) investigators (11) that the increased risk of breast cancer associated with the use of estrogen plus progesterone declines markedly soon after discontinuation of combined hormone therapy and is unrelated to changes in frequency of mammography (9). Controversies regarding the safety of hormone therapy have drawn attention to the need to search for other preventive or therapeutic alternatives especially for cardiovascular disease. A number of studies have demonstrated an increase in tension-generating capacity of myocardium induced by exercise training (16, 19, 37). A favorable beneficial impact of regular exercise has also been indicated in chronic heart failure (4). Bupha-Intr and Wattanapermpool (6) demonstrated the potential of exercise...
process of exercise training in preventing alterations of Ca\(^{2+}\) mobilization governed by SR activity following ovariectomy.

In experiments reported here, we demonstrated the cardioprotective ability of exercise training on SERCA expression, together with its regulatory protein phospholamban (PLB), and cytosolic Ca\(^{2+}\) removal activity in ovariectomized rats. We compared cardiac SR Ca\(^{2+}\) uptake function of intact and sex hormone-deprived female rats between moderate intensity treadmill-trained and sedentary groups.

**MATERIALS AND METHODS**

**Materials.** All chemicals were purchased from Sigma Chemical (St. Louis, MO) and USB (Cleveland, OH), electrophoretic reagents from BioRad (Hercules, CA) or Amersharm Pharmacia Biotech (Buckinghamshire, UK), and thapsigargin from Alomone (Jerusalem, Israel). \(^{45}\)CaCl\(_2\) was obtained from PerkinElmer (Boston, MA). Peroxidase-conjugated affinity donkey anti-mouse IgG (H+L) was purchased from Research Diagnostics (Flanders, NJ), and horseradish peroxidase-goat anti-rabbit IgG (H+L) conjugate (ZyMax grade) from Zymed (San Francisco, CA).

**Animal preparation.** Female Sprague-Dawley rats (8–9 wk old) weighing between 180 and 200 g were sham operated (Sham) or ovariectomized (OVX) and then randomly divided into sedentary and exercise training groups as previously described (6). Individual rats were housed in an 8×10 in. hanging cage provided with rat chow and water ad libitum. One week after surgery, a 9-wk running program on a motor-driven treadmill 5 times/wk was implemented in the exercised groups. During the first week of the program, rats were pretrained at a fixed speed of 21 m/min with 0% grade, with a varied running time from 2×5 min with a 10-min resting interval on day 1, reaching 2×25 min on day 5. From the second week to the end of the program, rats were subjected to 2×30 min of running at a fixed speed of 21 m/min with 7.5% and 5.5% grade for Sham and OVX groups, respectively. The exercise intensities were calculated for a work rate of 65–75% maximum oxygen consumption on the basis of body weight as previously described (6). Adequacy of the running program was verified by citrate synthase activity of plantaris muscle dissected on the day rats were killed. Animal protocol was approved by the Experimental Animal Committee, Faculty of Science, Mahidol University, in accordance with National Laboratory Animal Centre, Thailand.

**SR Ca\(^{2+}\) uptake measurement.** Left ventricular homogenate was prepared and used for determining oxalate-sustained SR \(^{45}\)Ca\(^{2+}\) uptake as described (7). In brief, left ventricle was homogenized in 20 mM imidazole for 30 passes in a Teflon-glass homogenizer, followed by filtration through six layers of cheesecloth. To the homogenate (1 mg/ml) was added various concentrations of Ca\(^{2+}\) ranging from pCa \((-\log([Ca^{2+}]))\) 8.0 to 4.875 together with 0.1% \(^{45}\)CaCl\(_2\). ATP (5 mM final concentration) was added to start Ca\(^{2+}\)-uptake reaction, which was incubated for 3 min at 37°C with shaking and stopped by rapid cooling in ice. An aliquot of the reaction mixture was filtered through 0.45-µM Millipore filter (Millex HA), and an equal amount of the filtrate and the nonfiltered solution were quantified for radioactivity. The amount of Ca\(^{2+}\) uptake was determined by subtracting radioactivity of the filtrate from that of the nonfiltrate. Nonspecific binding was determined at pCa 5.0 in the absence of ATP. Protein concentration was determined by Bradford assay.

**SERCA activity.** SR membrane was prepared from left ventricle as previously described (7). SR-enriched membrane suspension was immediately frozen and stored at –80°C until use. Protein concentration of SR vesicles was determined by Bradford assay. SRCA activity was determined by a triple enzyme assay (10). In brief, the assay was performed in various concentrations of Ca\(^{2+}\) ranging from pCa 8.0 to 5.0, pH 7.0, at 37°C. Five micrograms of SR-enriched vesicle protein were added to a 1-mL reaction mixture containing (in mM): 21 MOPS, 0.06 EGTA, 100 KCl, 3 MgCl\(_2\), 0.2 NADH, 1 phosphoenolpyruvate, 8.4 U pyruvate kinase, and 12 U lactate dehydrogenase. ATPase reaction was started by the addition of 1 mM ATP. SERCA activity was determined from linear kinetic reaction of NADH degradation monitored at 340 nm (UV 2550 spectrophotometer, Shimadzu, Japan). Nonspecific SERCA activity was determined in reaction mixture of pCa 5.0 containing 0.1 μM thapsigargin.

**Immunoblot analysis.** Frozen left ventricular tissue was homogenized in RIPA buffer containing various phosphatase and protease inhibitors as previously described (7). Protein concentration of the left ventricular homogenate was determined by bicinchoninic acid assay. Monoclonal antibodies against SERCA2 (1:1,000) and PLB (1:5,000) (Affinity Bioreagents, Golden, CO) were used for quantifying protein content of SERCA and phospholamban, respectively, in 100 μg of tissue homogenate. The proportion of monomer to pentamer PLB forms was also analyzed. Polyclonal antibodies against phosphorylated Ser\(^{16}\) (phospho-Ser\(^{16}\); 1:20,000) and phospho-Thr\(^{17}\) PLB (1:5,000; Badrilla, Leeds, UK) were used for determining amounts of phosphorylated Ser\(^{16}\) and phospho-Thr\(^{17}\) PLB, respectively, in nondegenerated preparations. The total amount of immunoblotted protein was determined relative to the amount of calseequstrin or actin. Band density was analyzed using Image Master Labscan version 3.01 and Image Master Totallab version 1.0 (Amersham Pharmacia Biotech).

**General and statistical analysis.** Curves relating pCa and SR Ca\(^{2+}\) uptake or SERCA activity were fitted to Hill equation using nonlinear least squares regression analysis (GraphPad Prism) to derive EC\(_{50}\) (half-maximal activating calcium concentration) and Hill coefficient. Data were presented as means ± SE. Significance of difference among groups of animals was analyzed using one-way ANOVA followed by the Student-Newman-Keuls test for multiple comparisons. P value <0.05 is considered significantly different among groups.

**RESULTS**

Table 1 summarizes heart, body, uterine, and soleus weights of sedentary Sham, exercised Sham, sedentary OVX, and exercised OVX animals. Compared with sedentary group, exercised rats demonstrated a significant increase in heart weight and heart per body weight. Exercise training increased body weight in Sham but not in OVX rats. As expected, uterine weight was significantly suppressed in OVX compared with Sham rats. Although there was no hypertrophy of soleus muscle among groups, citrate synthase activity was significantly induced in the exercised groups.

The effect of exercise training on cardiac SR Ca\(^{2+}\) uptake activity in OVX condition was first evaluated by determining oxalate-sustained SR \(^{45}\)Ca\(^{2+}\) uptake of left ventricular homogenate at various concentrations of calcium activation. Maximum SR Ca\(^{2+}\) uptake activity was significantly suppressed in OVX rat heart compared with Sham control (Fig. 1, A and B). A significant leftward shift in the pCa-Ca\(^{2+}\) uptake relationship representing an increased sensitivity of SR Ca\(^{2+}\) uptake function was also demonstrated in OVX rat heart (EC\(_{50}\) = 0.46 ± 0.01 μM) compared with Sham (0.57 ± 0.01 μM; Fig. 1, C and D). On the other hand, the exercise program did not exert any effect on maximum SR Ca\(^{2+}\) uptake activity in hearts of Sham groups (88.2 ± 2.4 and 89.5 ± 4.5 nmol·mg protein\(^{-1}\)·min\(^{-1}\) in sedentary and exercised groups, respectively), but significantly increased the suppressed maximum activity in OVX groups (72.4 ± 3.2 and 88.5 ± 3.6 nmol·mg protein\(^{-1}\)·min\(^{-1}\) in sedentary and exercised groups, respectively; Fig. 1, A and B). Similar changes were also observed in SR Ca\(^{2+}\) uptake activity in sham-operated groups (72.4 ± 3.2 and 88.5 ± 3.6 nmol·mg protein\(^{-1}\)·min\(^{-1}\) in sedentary and exercised groups, respectively).
uptake sensitivity (Fig. 1, C and D). SR Ca\(^{2+}\) uptake sensitivity in hearts of OVX rats with exercise training (EC\(_{50}\) = 0.59 ± 0.02 μM) was significantly higher than that in sedentary OVX rats (0.46 ± 0.01 μM), while exercise training in Sham groups induced no effect. To further clarify the impact of exercise training on cardiac SR Ca\(^{2+}\) uptake following ovariectomy, SERCA activity was assessed using a triple enzyme assay. A similar effect of exercise training on SERCA to that of SR Ca\(^{2+}\) uptake activity was observed in OVX animals. Exercise training in OVX rats

<table>
<thead>
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<th>Parameter</th>
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<th>Exercised</th>
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<td>352±9*</td>
<td>296±4*#</td>
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<td>0.130±0.004*</td>
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<td>% Heart/body wt</td>
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<td>0.28±0.01*</td>
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<tr>
<td>% Soleus/body wt</td>
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<td>CS activity, μmol·g(^{-1})·min(^{-1})</td>
<td>41.7±1.4</td>
<td>42.0±1.5</td>
<td>61.5±1.3*†</td>
</tr>
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Values are means ± SE of 16 rats. Sham, sham-operated controls; OVX, ovariectomized rats; CS, citrate synthase. *P < 0.05, †P < 0.05, significantly different from sedentary-sham and sedentary-ovariectomized rats, respectively.

Fig. 1. Effects of ovariectomy and exercise training on rat sarco(endo)plasmic reticulum (SR) Ca\(^{2+}\) uptake (A) and percent maximum SR Ca\(^{2+}\) uptake (C) of left ventricular homogenate at various Ca\(^{2+}\) concentrations on maximum SR Ca\(^{2+}\) uptake (B) and on EC\(_{50}\) (D). pCa ranged from 7.5 to 4.875, pH 7.0, and results from exercised sham group are not shown but would be superimposed on graph of sedentary sham group. Data are means ± SE from 14–16 preparations.

*Significantly different from sedentary sham (P < 0.05) using Student-Newman-Keuls test after ANOVA. SHAM, sham control; OVX, ovariectomized; Ex., exercised; Sed., sedentary.
restored both suppressed maximum SERCA activity (1.04 ± 0.04 μmol Pi·mg protein⁻¹·min⁻¹) and increased SERCA sensitivity (EC₅₀ = 0.64 ± 0.04 μM) to 1.29 ± 0.05 and 0.98 ± 0.06 μmol Pi·mg protein⁻¹·min⁻¹, respectively, which remained unchanged in sedentary Sham controls (Fig. 2). SERCA expression correlated with maximum SERCA activity, which was not affected by exercise training in the Sham group but significant upregulation in OVX rats toward Sham control level (Fig. 3, A and B). No effect of exercise training or female sex hormones was observed on PLB expression (Fig. 3, A and C). Changes in SERCA-to-PLB ratio confirmed that exercise training upregulated expression of SERCA that had been suppressed by female sex hormone deficiency (Fig. 3D).

As both amount and activity of phosphorylated PLB are responsible for its inhibitory function on SERCA, we therefore determined whether exercise training influenced phosphorylation level and isomeric forms of cardiac PLB of OVX rats. While PLB phosphorylation at Ser¹⁶ is not different among the groups (Fig. 4, A and B), phospho-Thr¹⁷ PLB is significantly suppressed in sedentary OVX rats, which was restored to control level by exercise training, but this was not seen in Sham rats (Fig. 4, A and C). There was ~10% shift in the proportion of monomeric to pentameric cardiac PLB of OVX rats, and the proportion of monomeric PLB was enhanced from 10.3 ± 0.7% in Sham to 21.4 ± 0.8% in OVX rats, which was reversed by exercise training, a phenomenon not present in the Sham groups (Fig. 5).

DISCUSSION

This study demonstrated a similarity in the impact of exercise training and female sex hormones on regulating cardiac SR Ca²⁺ uptake activity through activation of SERCA. The results lend significance to exercise training as a low-risk cardioprotective alternative to hormone replacement therapy in menopause.

Enhancement of SR Ca²⁺ uptake activation is one drug therapy strategy for cardiac failure (14, 25). Exercise training is also a well-accepted procedure for cardiac rehabilitation and prevention of heart disease (3). Results from the present study have provided evidence of similar effectiveness of exercise training to that of hormone replacement in maintaining the SR Ca²⁺ uptake function of ovarioctomized cardiomyocytes. It is, however, of interest to note that moderate intensity of regular exercise exerts no impact on SR Ca²⁺ uptake function of healthy rat heart but has a preventive effect in ovarioctomized rats.

![Fig. 2. Effects of ovariectomy and exercise training on rat SERCA activity (A) and percent maximum SERCA activity (C) of cardiac SR vesicles at various calcium concentrations, on maximum SERCA activity (B) and on EC₅₀ (D), pCa ranged from 7.5 to 5.0, pH 7.0. Data are means ± SE from 11–13 preparations. *Significantly different from sedentary sham (P < 0.05) using Student-Newman-Keuls test after ANOVA.](http://jap.physiology.org/)

![Fig. 2](http://jap.physiology.org/)
heart. This suggests an intracellular homeostatic maintenance of SR Ca\(^{2+}\) through either the function of SR Ca\(^{2+}\) uptake or SERCA under physiological stress. The indication is indirectly supported by data showing a reduced life span with pathologically hypertrophic induction either in transgenic reduction of SERCA affinity for Ca\(^{2+}\) (32) or in transgenic-induced Ca\(^{2+}\) hypersensitivity of SERCA models (34).

Unaltered SR Ca\(^{2+}\) uptake and SERCA expression in normal cardiomyocytes following moderate exercise stress for 8 wk in our study are in the same line as most previous reports using mild to moderate intensities with various durations of exercise training program (13, 15, 24, 30). A study of cardiac SR Ca\(^{2+}\) uptake function in rats using half-time of [Ca\(^{2+}\)]\(_{i}\) transient decline as an indicator also demonstrated lack of changes in SR Ca\(^{2+}\) uptake activity after sprint training (38). Only in studies using a high-intensity exercise program have significant increases in cardiac SERCA expression been demonstrated (36, 37). These results suggest that exercise intensity affects SERCA expression, a notion supported by a study in skeletal muscle in which the SERCA mRNA level paralleled increased exercise intensity (21). In any case, the moderate-intensity regular physical activity, a public health recommendation issued by the American College of Sports Medicine and the American Heart Association (17), could undoubtedly improve SERCA function in female sex hormone-deficient condition as demonstrated in the present study and under many pathological insults in which SR Ca\(^{2+}\) uptake is also impaired (13, 24, 30).

In general, the ability of SERCA to pump Ca\(^{2+}\) into SR could be affected by either a change in quantity (turnover) or quality (maximum activity or sensitivity to Ca\(^{2+}\)) of protein activity. Exercise training has minimal effect on SERCA function under normal physiological conditions but exerts an enhanced action under pathological conditions. Similar magnitudes of SERCA downregulation have been detected in ovariectomized (~26%; Ref. 7), aged (~31%; Ref. 18), and infarcted (~25%; Refs. 36, 38) rat hearts, all of which could be prevented by exercise training. It is, however, still unclear as to how exercise training causes cardiac SERCA activation, although results of present and previous studies indicate that exercise training and ovarian sex hormones may share part of the action. Changes in physiological signals brought on by exercise training may underline the effects of regular exercise on SERCA gene expression. Although induction of adrenergic signals by exercise training is a good candidate (2), we have demonstrated previously that deficiency of female sex hormones induces upregulation of cardiac β\(_1\)-adrenoceptors, which can be restored by either hormone replacement or exercise training (6, 33). The increase in SERCA activity by high-intensity training exercise in ovarian sex hormone-intact condition mentioned earlier suggests an involvement of non-sex
hormone-related signals in regulating cardiac SR Ca\(^{2+}\) uptake function.

In addition to alterations in SERCA expression, exercise training may induce qualitative changes in SERCA activity through phosphorylation and/or polymerization of PLB. Phosphorylation of PLB releases its interaction with SERCA resulting in a more kinetically active state of the SERCA pump (12, 35). PLB phosphorylation also promotes oligomerization of PLB monomers into pentamers and thus stimulating SERCA function. We detected no change of either phospho-Ser\(^{16}\) or phospho-Thr\(^{17}\) PLB in sham-operated rats after regular exercise, although increases in cardiac phospho-Thr\(^{17}\) PLB have been reported in exercise-trained animals (20, 30). This could be due to the differences in duration and intensity of training exercise used in these various studies. On the other hand, suppression of cardiac phospho-Thr\(^{17}\) PLB in ovariectomized rats shown in this study as well as in spontaneous hypertensive rats previously reported (22, 29) could be reversed by exercise training. Although there was no evidence of the effect of exercise training on PLB oligomerization status, nevertheless our data clearly demonstrated the effectiveness of regular exercise on maintaining monomer-pentamer equilibrium of PLB after ovarian sex hormone deficiency. Our findings that exercise training increased phospho-Thr\(^{17}\) and pentameric PLB levels in ovariectomized rat heart provide additional information to the general concept (26, 39) in explaining exercise-induced restoration of SR Ca\(^{2+}\) uptake sensitivity.

In summary, exercise training demonstrates an alternative to female sex hormones in reducing heart disease risk by maintaining homeostasis of various subcellular and molecular functions of cardiomyocytes. Female sex hormones clearly influence cardiac improvement through SR Ca\(^{2+}\) uptake activity in response to exercise training. Together with the protective role

![Fig. 4. Immunoblot blot analysis of rat phospho-Ser\(^{16}\) and phospho-Thr\(^{17}\) PLB from left ventricular homogenate. A: immunoblot; B: ratio of phospho-Ser\(^{16}\) PLB to actin; C: ratio of phospho-Thr\(^{17}\) PLB to actin. Data are mean ± SE from 6 hearts. *Significantly different from sedentary sham (P < 0.05) using Student-Newman-Keuls test after ANOVA.](https://jap.physiology.org/)

![Fig. 5. Immunoblot blot analysis of rat monomeric and pentameric forms of PLB from left ventricular homogenate. A: immunoblot; B: percent monomeric PLB; C: percent pentameric PLB. Data are mean ± SE from 6 hearts. *Significantly different from sedentary sham (P < 0.05) using Student-Newman-Keuls test after ANOVA.](https://jap.physiology.org/)
of female sex hormones, regular exercise of moderate intensity appears to enhance myocardial performance by induction of hypertrophy without affecting Ca\(^{2+}\) removal activity of SR. The molecular impacts underlying cardioprotective activity of exercise training and female sex hormones include regulation on SERCA expression and PLB phosphorylation.

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References


