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ORIGINAL PAPER

Regular exercise modulates cardiac mast cell activation in ovariectomized rats

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Abstract It is well accepted that regular exercise is a significant factor in the prevention of cardiac dysfunction; however, the cardioprotective mechanism is as yet not well defined. We have examined whether regular exercise can modulate the activity of cardiac mast cells (CMC) after deprivation of female sex hormones, as well as the density and percentage degranulation of mast cells, in ventricular tissue of ovariectomized (OVX) rats after an 11-week running program. A significant increase in CMC density with a greater percentage degranulation was induced after ovarian sex hormone deprivation. Increased CMC density was prevented by estrogen supplements, but not by regular training. To the contrary, increased CMC degranulation in the OVX rat heart was attenuated by exercise training, but not by estrogen supplement. These findings indicate a significant correlation between the degree of CMC degranulation and myocyte cross-section area. However, no change in the expression of inflammatory mediators, including chymase, interleukin-6, and interleukin-10, was detected. Taken together, these results clearly indicate one of the cardioprotective mechanisms of regular aerobic exercise is the modulation of CMC activation.

Keywords Estrogen · Chymase · Interleukin-6 · Interleukin-10

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Introduction

Regular exercise is highly recommended in post-menopausal women for its beneficial effects on cardiac function, whether or not they eventually receive hormone replacement therapy. It is well known that regular exercise reduces the risk of heart disease and hypertension, but basic information regarding the mechanism of action of cellular activation in the heart remains incompletely understood [8, 25, 32]. The activation of mast cells (MCs) has recently been shown to be a key event in the induction of pathologic hypertrophy by volume overload or pressure overload [19, 23]. Patients with dilated cardiomyopathy have been found to have an increased density of cardiac mast cells (CMCs) [31, 34], as well as a twofold higher percentage degranulation of CMCs compared to normal hearts [31]. MC density has been demonstrated to be enhanced by two- to threefold in animal models of pressure overload or volume overload, coupled with an increase in chymase activity [19, 23]. The impact of MCs on cardiac remodeling is supported by evidence that MC stabilization effectively prevents volume overload-induced dilated cardiac hypertrophy [7]. Moreover, MC stabilizers and chymase inhibitors can attenuate cardiac hypertrophy and decrease the cardiac contraction induced after aortic constriction [19]. A rather large body of evidence suggests that MC activation is a critical step in pathologic cardiac remodeling. Several studies have demonstrated that regular exercise can attenuate such pathologic remodeling [10, 40] and that regular exercise might be able to modify MC activation.

Previously reported studies from our research team have shown that regular exercise can prevent all of the cardiac contractile changes that resemble those seen upon estrogen supplementation in ovariectomized (OVX) rats [8, 9]. Based on these results, we proposed that regular exercise

and estrogen share the same mode of activation of cardioprotective signaling. Recent reports on estrogen-based regulation of CMC activation [19, 23, 37] has led us to hypothesize that regular exercise might also modulate CMC activity. In two of these studies, the presence of female sex hormones was able to prevent the left ventricular hypertrophy and increased CMC density induced after volume overload [23], and estrogen supplementation attenuated increases in MC density and chymase release in the hearts of OVX rats after transverse aortic constriction [19]. In the third study, increases in MC density and chymase expression in the hearts of mRen2.Lewis rats after OVX were abolished using a G protein-coupled estrogen receptor agonist [37]. It would therefore appear that cardiac changes in the absence of female sex hormones might be due (at least in part) to increased CMC activation. This in turn suggests the possibility that the mechanism underlying the cardioprotective effects of regular exercise in ovarian sex hormone-deprived conditions could result from CMC stabilization.

The aim of our study was to test whether regular exercise inhibited CMC activation after deprivation of female sex hormones in a rat model. OVX rats were subjected to a 10-week running program, during which time CMC density, percentage degranulation of CMCs, and levels of various inflammatory chemokines were evaluated and correlated with myocardial changes.

Materials and methods

Materials

All chemicals were purchased from Sigma Chemical (St. Louis, MO), and electrophoretic reagents were purchased from Bio-Rad (Hercules, CA), Amersham Pharmacia Biotech (Buckinghamshire, UK), Omnipur (EMD Millipore, Billerica, MA) or Thermo Scientific (Waltham, MA).

Animals and treatment

The animal protocol was approved by the Experimental Animal Committee, Faculty of Science, Mahidol University, in accordance with the guidelines of the National Laboratory Animal Center, Thailand based on "The guide for the care and use of laboratory animals, 8th edition" (NIH). Female Sprague-Dawley rats (8–9 weeks old) were ovariectomized or sham operated. One week after surgery, OVX rats were randomly divided into three treatment groups for vehicle injection, estrogen supplementation and regular exercise, respectively. The lack of female sex hormones was confirmed by the reduced uterine weight at the end of study. All animals were fed ad libitum (Betagro Public Co., Ltd., Bangyor, Thailand) and had access to tap water during the entire experiment. Each rat was housed individually under a 12:12 light/dark cycle with temperature and humidity control. Estrogen supplementation was started by subcutaneous injection of 0.1 mL of estrogen (5 μg/rat) 3 days per week as previously described [38]. In the sham and OVX controls, 0.1 mL of corn oil was injected as placebo.

The regular exercise program including a 1-week acclimatization period followed by 10 weeks of moderate intensity running (65–75 % maximum oxygen consumption) as previously described [9]. Each rat in the regular exercise group was made to run for two 30-min periods per day, 5 days per week, with a 10- to 15-min rest period between each exercise period. Adequacy of the running program was verified by echocardiography at the end of study.

Cardiac structure and function by assessed by echocardiography

The echocardiographic study was performed as previously described [20]. Briefly, rats were anesthetized with intraperitoneal pentobarbital sodium (50 mg/kg body weight). Using an echocardiography machine (Samsung Medison, Seoul, Korea) equipped with a 10-MHz echocardiographic probe (10 MHz), we scanned the chest wall using two-dimensional short-axis view at the mid-papillary muscle in M-mode. Used the modified recommendations off the American Society for Echocardiography, we measured the interventricular septum (IVS), left ventricular posterior wall (LVPW), diameter of the internal left ventricle (LVID), LV mass, relative wall thickness, and percentage of fractional shortening for least three consecutive cardiac cycles on the M-mode tracings. LV mass was calculated using the following formula [20]:

$$\text{LV mass} = 1.04 \times [(\text{LVID}_\text{d} + \text{LVPW}_\text{d} + \text{IVS}_\text{d})^3 - \text{LVID}_\text{d}^3]$$

To confirm the hypertrophy of the heart, heart weight per body weight was also determined. In addition, the cardiomyocyte cross-section area was measured on myocardial histological sections stained with hematoxylin and eosin stain.

MC density and morphological changes

After echocardiography examination, the rat was sacrificed and the heart was excised and perfused with Ca^{2+}-free Krebs–Henseleit solution before being fixed in 10 % formalin and embedded in Paraffin. The sample was then sectioned on a microtome (thickness 5 μm) and the sections placed on microscope slides. To stain the MCs, rehydrated

tissue sections were first stained with 0.001 g/mL of toluidine blue for 3 and then rinsed twice in distilled water to wash out the dye before dehydration. Counting was performed on a whole section at a magnification of 100×. The density of MCs was expressed as the mean number of mast cells per square millimeter of tissue section. The MCs were distinguished from other inflammatory cells as previously described [43]. Degranulated MCs were identified by extruded granules and the appearance of ruptured cell membranes or irregular border as granules are released from the cytoplasm. The result was expressed as the percentage of degranulated MCs per total number of MCs.

Immunoblot analyses

Frozen ventricular muscle tissue was mixed and homogenized with extraction sample buffer (50 mM Tris pH 6.8, 2.5 % SDS, 10 % glycerol, 1 mM dithiothreitol, 1 μg/mL leupeptin, 1 μg/mL pepstatin A, 1 mM phenylmethylsulfonyl fluoride) and then subjected to sodium dodecyl

Table 1 General characteristics of sham-operated rats and ovariectomized rats receiving sham injection, estrogen supplementation or exercise training[a]

Parameters	Sham-operated group (n = 6 rats)	Ovariectomized rats		
		Oil injection (n = 8 rats)	Estrogen supplementation (n = 7 rats)	Exercise regimen (n = 7 rats)
Body weight (BW) (g)	268 ± 5	363 ± 9*	256 ± 7$^{\#}$	342 ± 9*
Heart weight (HW) (g)	1.31 ± 0.05	1.45 ± 0.03*	1.33 ± 0.04$^{\#}$	1.55 ± 0.03*
HW/BW (100×)	0.490 ± 0.017	0.400 ± 0.013*	0.518 ± 0.011$^{\#}$	0.456 ± 0.013$^{\#}$
Tibial length (TL) (cm)	4.15 ± 0.02	4.49 ± 0.03*	4.19 ± 0.03$^{\#}$	4.39 ± 0.03$^{*,\#}$
HW/TL (g/cm)	0.316 ± 0.012	0.322 ± 0.007	0.317 ± 0.011	0.354 ± 0.008
Soleus weight (g)	0.112 ± 0.002	0.146 ± 0.004*	0.098 ± 0.007	0.139 ± 0.005*
Uterine weight (g)	0.602 ± 0.054	0.154 ± 0.015*	0.618 ± 0.036	0.173 ± 0.025*

$^{*,\#}$ $P < 0.05$, significantly different from Sham-operated rats and ovariectomized (OVX) rats, respectively, using the Student–Newman–Keuls test after analysis of variance (ANOVA)

Data are presented as the mean ± standard error of the mean (SEM)

[a] There were 3 treatment groups for OVX rats: vehicle (0.1 mL corn oil) injection (OVX control group), estrogen supplementation and regular exercise, respectively. In the sham-operated group, 0.1 mL corn oil was also injected as placebo

Table 2 Echocardiographic parameters of sham-operated rats and ovariectomized rats and receiving sham injection, estrogen supplementation or exercise training

Parameters	Sham-operated	Ovariectomized rats		
		Oil injection	Estrogen supplementation	Exercise regimen
IVS_S (cm)	0.233 ± 0.007	0.240 ± 0.011	0.258 ± 0.014	0.261 ± 0.006
IVS_D (cm)	0.175 ± 0.007	0.190 ± 0.014	0.193 ± 0.017	0.208 ± 0.007
$LVPW_S$ (cm)	0.232 ± 0.009	0.282 ± 0.024	0.280 ± 0.026	0.302 ± 0.026
$LVPW_D$ (cm)	0.143 ± 0.014	0.201 ± 0.018	0.186 ± 0.016	0.183 ± 0.013
$LVID_S$ (cm)	0.373 ± 0.012	0.414 ± 0.022	0.314 ± 0.025$^{\#}$	0.367 ± 0.015
$LVID_D$ (cm)	0.588 ± 0.020	0.602 ± 0.037	0.523 ± 0.030	0.615 ± 0.015
LV FS (%)	36.6 ± 0.3	30.9 ± 0.6*	39.9 ± 1.0$^{*,\#}$	40.5 ± 1.2$^{*,\#}$
LV EF (%)	72.5 ± 0.4	64.8 ± 0.8*	76.6 ± 1.2$^{*,\#}$	76.7 ± 1.3$^{*,\#}$
RWT	0.463 ± 0.052	0.680 ± 0.092	0.728 ± 0.097	0.603 ± 0.058
Estimated LV mass (g)	0.541 ± 0.023	0.789 ± 0.063*	0.614 ± 0.045$^{\#}$	0.817 ± 0.016*
LV mass index	2.08 ± 0.11	2.04 ± 0.12	2.25 ± 0.08	2.51 ± 0.11$^{*,\#}$

$^{*,\#}$ $P < 0.05$, significantly different from Sham-operated rats and OVX rats, respectively, using Student–Newman–Keuls test after ANOVA

Data are presented as the mean ± SEM

IVS_S, *IVS_D* Systolic and diastolic parameters, respectively, of the interventricular septum (*IVS*), *$LVPW_S$*, *$LVPW_D$* systolic and diastolic parameters, respectively, of the left ventricular posterior wall (*LVPW*), *$LVID_S$*, *$LVID_D$* systolic and diastolic parameters, respectively, of the left ventricular internal diameter (*LVID*), *FS* fractional shortening, *EF* ejection fraction, *RWT* relative wall thickness, *LV* left ventricular

sulfate-polyacrylamide gel electrophoresis. The separated proteins were transferred onto PVDF membranes. Rabbit anti-rat interleukin-6 (IL-6; 1:1,000), rabbit anti-rat IL-10 (1:1,000), and anti-MCl chymase antibody-C-terminal (1:2,500) were obtained from Abcam (Cambridge, UK). Anti-β-actin antibody (1:5,000) was purchased from AVIVA Systems Biology (San Diego, CA). The secondary antibody used was goat anti-rabbit immunoglobulin G (1:10,000) from Zymed (San Francisco, CA). Band density was analyzed using Labscan version 5.0 (Amersham Biosciences) and ImageQuant TL version 7.0 (GE Healthcare Life Sciences, Cleveland, OH).

Data and statistical analysis

All data are presented as the mean ± standard error of the mean (SEM). For comparisons of four groups, one-way analysis of variance was used, and if statistically significant differences were detected, the Student–Newman–Keuls test was applied to further identify groups with different means. Differences were considered statistically significant at $P \leq 0.05$.

Results

General characteristics which could be attributed to the lack of ovarian sex hormones and regular exercise, respectively, are presented in Table 1. Deprivation of female sex hormones was confirmed by a marked decrease in uterine weight in OVX rats and OVX rats that were subjected to the regular exercise regimen. The 10-week deficiency of ovarian sex hormones resulted in an increase in body weight and heart weight, but the hypertrophic index by heart per body weight was decreased significantly (0.400 ± 0.013) as compared with sham controls (0.490 ± 0.017). Estrogen supplementation prevented changes in heart weight and body weight, but regular exercise could improve the heart per body weight ratio compared with sedentary OVX rats without any significant change in body weight.

Cardiac hypertrophy due to regular aerobic exercise was confirmed by the echocardiography (Table 2) and histochemistry studies (Fig. 1). Deprivation of ovarian sex hormones had no effect on hypertrophy of the LV, but significant decreases in the left ventricular ejection fraction and fractional shortening were observed in OVX rats. Reduction in cardiac contractility could be prevented by estrogen supplementation or regular exercise. Female sex hormones had no effect on the cross-section areas of cardiomyocytes, whereas the increased cross-section area of cardiomyocytes in exercise groups confirmed the hypertrophic effect of exercise.

Specific histochemical staining techniques revealed that chronic deprivation of female sex hormones increased CMC density compared with the sham control (3.13 ± 0.18 vs. 1.89 ± 0.12 cells/mm^2; Fig. 2). The lack of female sex

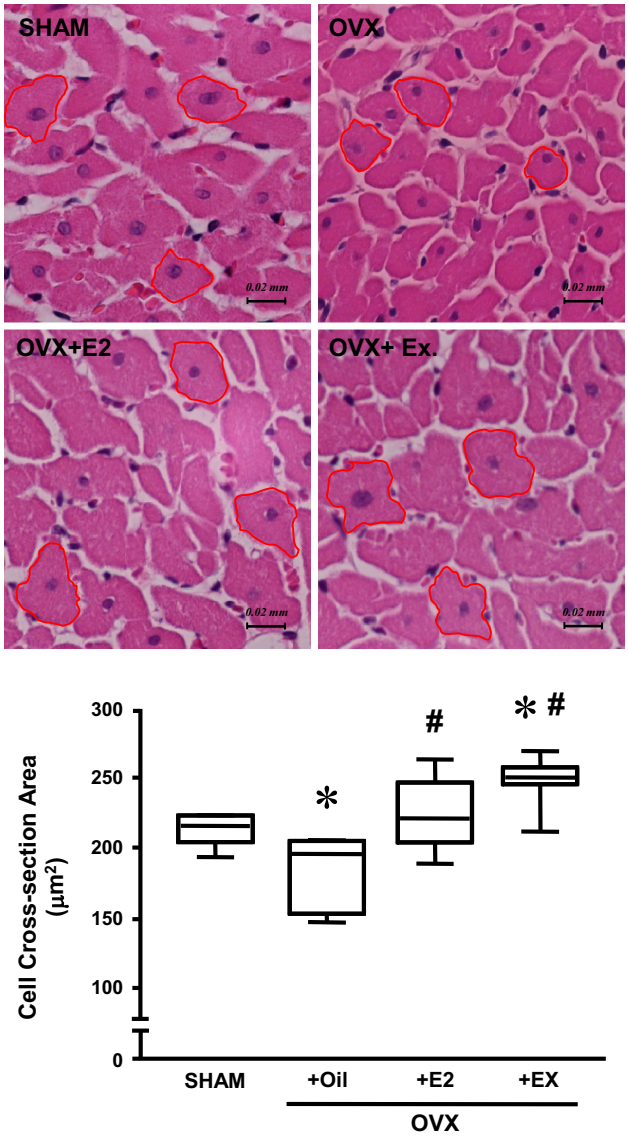

Fig. 1 Effect of regular exercise on cardiomyocyte cross-sectional area in ovariectomized (*OXV*) rats. *Stained images* are transverse sections of cardiomyocytes at ×400 magnification from the hearts of sham-operated controls (*SHAM*) and OXV rats with no further treatment (*OXV*), with estrogen supplementation (*OVX + E2*), or with exercise training (*OVX + Ex*). Only myocytes with a nucleus, a clear cell boundary, and a round or rectangular shape (length:width <1.5) were collected. *Box plot* of cross-sectional area of cells from the Sham-operated (control) group (*SHAM*) and from the three treatment groups of OXV rats (*+oil*, *+E2*, *+EX*). *Top* and *bottom* of *box* Minimum and maximum levels of cell cross-sectional area, *horizontal line within the box* median. Data are from 6–7 hearts in each group (150 cells per heart). *Asterisk* and *hash symbols* Significant difference ($P < 0.05$) from SHAM and OVX rats, respectively, using the Student–Newman–Keuls test after analysis of variance (ANOVA)

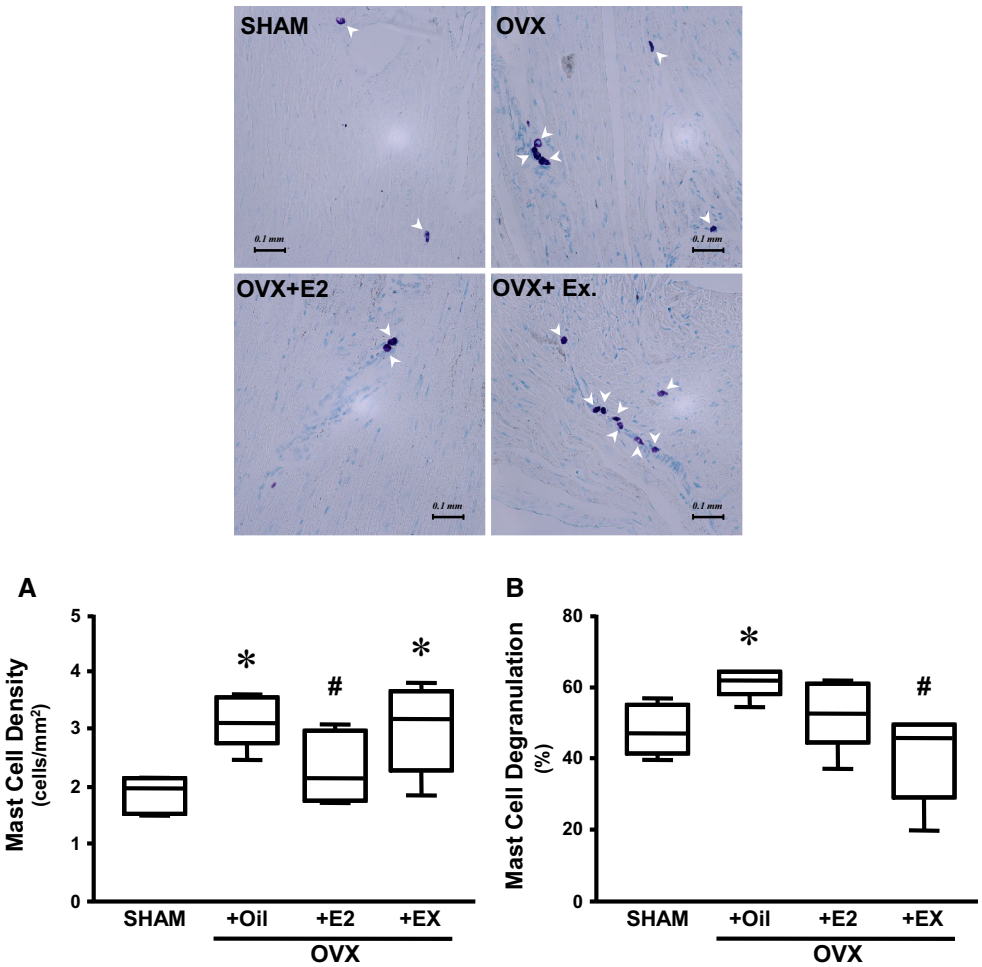

Fig. 2 Effect of regular exercise on the density (**a**) and percentage of degranulation (**b**) of cardiac mast cells (MCs) in ovariectomized (*OVX*) rats. *Images* are transverse sections of the ventricle at ×40 magnification from sham-operated controls (*SHAM*) and from OXV rats with no further treatment (*OXV*), with estrogen supplementation (*OVX* + *E2*), or with exercise training (*OVX* + *Ex*). Cardiac MCs were identifiable by their dark-purple coloration (*arrowheads*) due to toluidine staining. *Box plot* of number of cardiac MCs per tissue area (**a**) and percentage MC degranulation (**b**) from the Sham-operated (control) group (*SHAM*) and from the three treatment groups of OXV rats (+*oil*, +*E2*, +*EX*). *Top* and *bottom* of *box* Minimum and maximum values, *horizontal line within the box* median. Data are from 6–7 hearts in each group. *Asterisk* and *hash symbols* Significant difference ($P < 0.05$) from SHAM and OVX groups, respectively, using the Student–Newman–Keuls test after ANOVA

hormones also increased the percentage degranulation of MCs (61.7 ± 1.5 vs. 48.3 ± 2.9 % of sham controls). Estrogen supplementation was able to completely prevent the increases in MC density (2.32 ± 0.24 cells/mm^2), but only partially attenuated percentage degranulation. Conversely, regular aerobic exercise could not prevent increases in MC number due to deprivation of female sex hormones, but it did significantly decrease the percentage degranulation of MCs significantly (40.8 ± 4.9 %). Thus, the number of degranulated CMCs in exercised OVX rats was similar to that in sham controls [1.18 ± 0.15 (exercise group) vs. 0.91 ± 0.07 cell/mm^2 (sham group)]. These findings suggest a protective regulatory effect of estrogen and regular exercise on CMC function.

We then evaluated whether changes in MC activation could be the cause of cardiac hypertrophy, as well as the relationship between MC density and cross-sectional area of cardiomyocytes (Fig. 3). We found no correlation between cross-sectional area of cardiomyocytes and total density of MCs or percentage MC degranulation ($r^2 = 0.0893$, $P = 0.1560$; $r^2 = 0.07847$, $P = 0.1849$, respectively), but the number of degranulated MCs was correlated significantly with cardiomyocyte size ($r^2 = 0.237$, $P = 0.0157$).

An immunoblotting technique was used to estimate the levels of chymase, a major protease released from MCs, in the heart as a measure of CMC activity (Fig. 4a). We found that the number of MCs after deprivation of sex hormones had increased, but chymase expression was not altered. An effect of regular exercise on chymase levels in cardiac tissue was not observed.

Interleukin (IL)-6 levels were measured in the search for a possible signaling mechanism underlying the role of MCs in the regulation of cardiac remodeling (Fig. 4b). Deprivation of ovarian sex hormones had no effect on the myocardial expression of IL-6. Surprisingly, however, IL-6 levels in the hearts of OVX rats that underwent estrogen supplementation fell significantly by 40 %. To the contrary, regular exercise had no effects on cardiac levels of IL-6. Based on previous evidence that increased IL-10 level may underlie the protective action of regular exercise [15, 28], we then evaluated IL-10 expression; however, we detected no change in IL-10 levels among the four experimental groups (Fig. 4c).

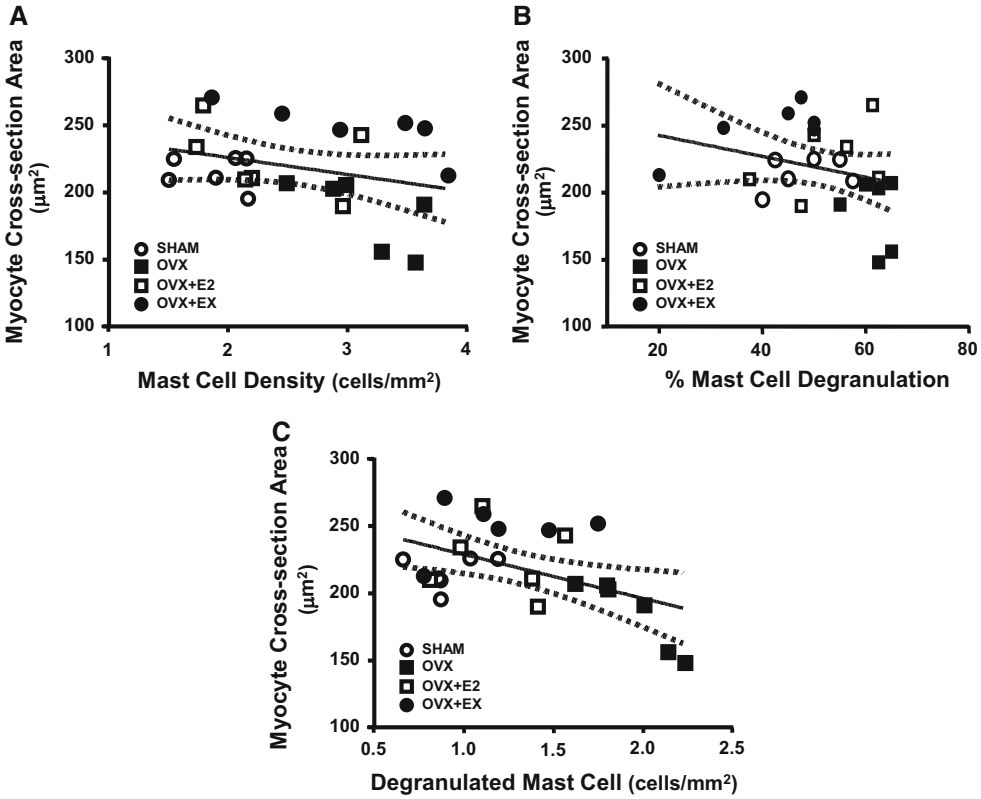

Fig. 3 Relationship between total cardiac MC density (**a**), percentage of MC degranulation (**b**), and degranulated MC density (**c**) to the cardiomyocyte cross-sectional area from all four experimental group combinations (see Fig. 1 caption for groups). Linear regression analysis indicated no relationship between cardiomyocyte cross-sectional area and total cardiac mast cell density ($r^2 = 0.08933$) or percentage of MC degranulation ($r^2 = 0.07847$), but a significant relation was found between degranulated MC density and cardiomyocyte size ($r^2 = 0.2376$)

Discussion

To our knowledge our study is the first to provide experimental evidence that chronic deprivation of ovarian sex hormones causes increases in the density and percentage degranulation of CMCs. In our rat model, estrogen supplementation had a major effect on the regulation of MC density, but regular exercise exerted a protective effect by inhibiting the increased degranulation of MCs. However, neither female sex hormones nor regular exercise appeared to have a regulatory impact on chymase expression in cardiac tissue. In addition, regular exercise had no effect on the expression of IL-6 and IL-10 proteins in the heart, but estrogen supplementation significantly suppressed IL-6 expression.

Female sex hormones (especially estrogen) are widely believed to be cardioprotective, but the mechanism of action and side effects of such protection are controversial [1, 29]. Female rats have been found to exhibit no adverse ventricular remodeling and to have a lower prevalence of mortality in response to volume overload than male rats [11]. This benefit of female sex hormones has been demonstrated to be due (at least in part) to an inhibition of MC activation by estrogen [23]. Estrogen and progesterone receptors are expressed in MCs [45]. Hence, whether MCs contribute to the cardiac changes after deprivation of sex hormones is an important question.

Information on the role of female sex hormones, especially estrogen, on cardiac hypertrophy is still largely inconclusive. Recent studies have found that estrogen regulates cardiomyocyte growth by inhibiting autophagy [13, 36] and that autophagy is associated with cardiomyocyte atrophy and therefore decreased contractility of the heart [21]. While it remains unclear at present whether cardiomyocyte autophagy is enhanced in the female sex hormone-deprived condition, an increase in osteocyte autophagy has been shown in OVX rats [41]. Exercise training-inhibited myocardial autophagy has also been demonstrated [39]. Importantly, the effect of MC activation, a key factor in our study, on cardiomyocyte autophagy has not yet been studied and further investigations in this area are needed.

Another potential protective mechanism of estrogen is the reduction of IL-6 activation. IL-6 is a pro-inflammatory cytokine that has been demonstrated to strongly regulate the proliferation and degranulation of MCs [16, 17]. Our observation of reduced IL-6 expression in OVX rats supplemented with estrogen strengthens the possibility that this hypothesis is correct. Several studies have confirmed the suppressive effect of estrogen on IL-6 levels in various tissues [18, 27]. However, the unexpected similarity of IL-6 levels in the heart between sham controls and OVX rats merits further discussion regarding the function of sex hormones. In a previous study we demonstrated that the

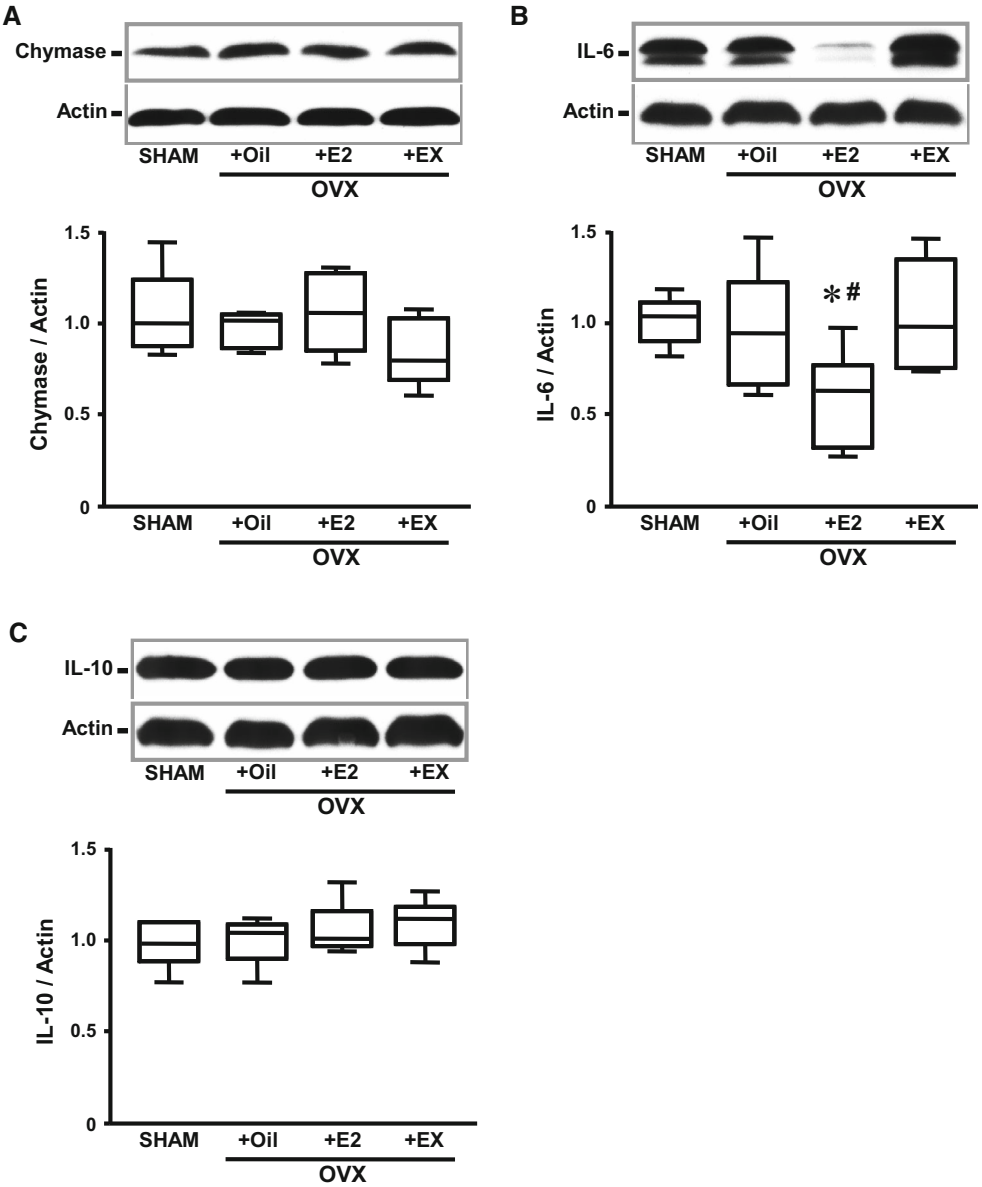

Fig. 4 Effect of regular exercise on the expression of inflammatory cytokines in the heart of OVX rats. Representative immunoblots of chymase (**a**), interleukin-6 (*IL-6*; **b**), and interleukin-10 (*IL-10*; (**c**) in comparison to β-actin expression are shown *above* the respective *box plots* (see Fig. 1 caption for groups). Data are the ratio of the density of each protein band to the density of the actin band from 6 hearts in each group. *Asterisk* and *hash symbols* Significant difference ($P < 0.05$) from SHAM and OVX groups, respectively, using the Student–Newman–Keuls test after ANOVA

dose of estrogen supplementation in OVX rats provided the same serum level of estrogen as that seen in sham-operated controls, leading us to conclude that a major difference is progesterone levels must be present [33]. Progesterone can reduce MC activity in various tissues [5, 35], but it increases IL-6 expression in mesenchymal stem cells [44]. Moreover, estrogen suppresses the levels of IL-6 and tumor necrosis factor (TNF)-α in monocytes, while progesterone increases TNF-α expression and has less of an effect on IL-6 expression [14]. Whether progesterone counteracts estrogen in regulating IL-6 expression in heart tissue is not yet known.

We previously proposed that regular exercise might regulate MC activation by inducing IL-10 production. IL-10 is an anti-inflammatory cytokine that can also inhibit MC activity [24]. Several studies have demonstrated that regular exercise can increase IL-10 levels in plasma and cardiac tissue [15, 28], possibly suggesting that IL-10 is an endogenous MC stabilizer activated by regular exercise. However, as the IL-10 levels were unchanged in our OVX rats subjected to the exercise regimen, the MC-suppressive effect of regular exercise observed in our study might be due to other pathways. One possible effect of exercise in preventing MC activation is through sympathetic activation. Epinephrine can inhibit the histamine release induced by antigens in passively sensitized human lungs [2]. Beta-2 adrenoceptor agonists also suppress the immunoglobulin E receptor-dependent release of histamine and inhibit the stem cell factor-induced proliferation and migration of MCs [12]. In addition, preconditioning with norepinephrine can

attenuate CMC degranulation induced by ischemia–reperfusion injury [30]. Therefore, regular sympathetic stimulation during exercise might be the underlying mechanism that inhibits MC degranulation. However, this hypothesis is counterbalanced by the increase in MC degranulation observed after a single dose of isoproterenol [22].

The results of our study also suggest that MCs are not involved in the induction of physiologic cardiac hypertrophy. Our hypothesis is supported by a study demonstrating that MC stabilizers cannot prevent the cardiac hypertrophy induced by norepinephrine infusion [6]. However, the inverse relationship between degranulated MCs and cross-sectional areas of cardiomyocytes suggests that MC activation might be associated with myocardial adaptation. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are potent stimulators of histamine release from peritoneal MCs [42]. Decreased levels of BNP upon endurance exercise training have been documented [4], so it is possible that MC degranulation is relatively reduced with exercise. However, the impact of ANP and BNP on CMCs is controversial [3, 26] and merits further investigation.

Conclusions

The results of this study demonstrate that estrogen and regular exercise have a differential effect on regulation of MC activation. An increase in MC activation after deprivation of ovarian sex hormones could be involved in the cardiac changes observed in postmenopausal women. These results also support implementation of regular aerobic exercise as an alternative to hormone replacement therapy in this population. Moreover, suppression of MC degranulation by regular exercise suggests that MC activation could be another indicator to differentiate between physiologic and pathologic cardiac hypertrophy.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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