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PHYSICAL INACTIVITY CAUSES ENDOTHELIAL DYSFUNCTION

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Recent studies have linked exercise training to increased bioavailability of vascular nitric oxide (NO) and to improved endothelial function in patients with cardiovascular disorders. The effects of physical inactivity on normal vascular endothelial function are not known. We speculated that an impairment of endothelial function may be a factor associated with a sedentary lifestyle in healthy individuals and investigated if physical inactivity impacts on endothelial function in young normal mice.

Materials and methods

Healthy male C57/Bl6 mice living in groups of 5 in large cages were randomly assigned to stay there or to live alone in small cages. Mice living in groups were fighting, running and climbing for the most part of their active daily cycle, while singularized mice were predominantly resting during their active daily cycle and showed a low physical activity. The time of singularization was 5 and 9 weeks. Some sedentary and moving mice underwent exercise program. Mice ran in a newly established self-build exercise treadmill especially designed for mice. After adaptation to training, mice were exercised for 3 weeks at 5 days a week for 30 minutes at 0.25 m/s. All mice completed the exercise protocol without signs of exhaustion. Within 16 to 20 hours after termination of the last training, mice were sacrificed by inhalation of carbon dioxide and their aortas, soleus muscle and hearts were immediately frozen in liquid nitrogen. The frozen tissues were taken to prepare total protein for endothelial NO synthase (eNOS) western blotting and to quantify the maximal citrate synthase activity.

Preparation of thoracic rings segments was performed in HEPES-containing Krebs-Henseleit buffer, while the organ bath experiments were done in the same buffer lacking HEPES. After a 60 minutes equilibration period, aortic rings were repeatedly subjected to 80 M KCl.

Function of endothelium was examined by cumulative addition of acethylcholine ACh (10^{-9}–10^{-5} M) following submaximal precontraction with phenylephrne (PE). In moving mice and those subjected to 5 weeks of singularization endothelium dependend vasodilation was followed by a cumulative application of PE (10^{-9}–10^{-5} M). Thereafter, the aortic rings were precontracted with 1 μM PE and a concentration-response curve for SNAP (10^{-9}–10^{-5} M) was performed.

Results

There was a significant increase of soleus and cardiac muscle muscle citrate synthase activity in moving and exercised mice as compared to sedentary mice and this increase was much more pronounced after exercise. In addition, the heart weight/body weight ratio (in mg/g) of sedentary mice (5.2±0.09) was increased in moving mice (5.5±0.1, $P<0.05$) and after 3 weeks of exercise (6.04±0.04, $P<0.01$).

Endothelial function of moving and sedentary mice was assessed by examination of endothelium-dependent vasodilation to ACh.

The concentration-response curves for ACh demonstrate that 5 and 9 weeks of forced physical inactivity results in endothelial dysfunction (Figure).

These data suggest that 5 weeks of physical inactivity is sufficient to induce a degree of endothelial dysfunction in mice that is not further ag-

gravated by prolonging the time period of physical inactivity.

Sedentary mice which underwent the exercise program regained their normal ACh response, while exercise had no effect on endothelium-dependent vasorelaxation in moving mice (Figure B).

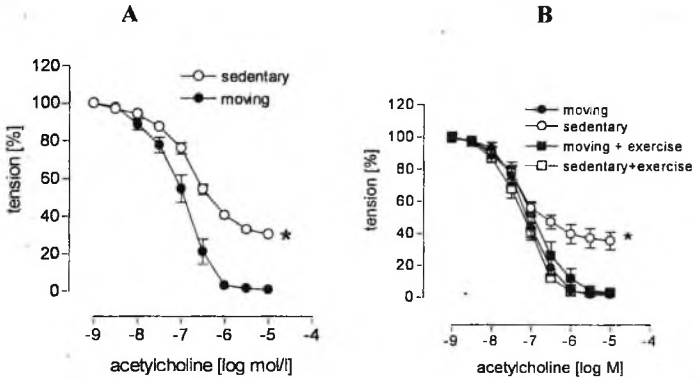

Figure. Endothelium-dependent vasodilation in aortic rings of sedentary mice after 5 (A) and 9 (B) weeks of singularization compared to moving mice and to sedentary and moving mice which underwent the exercise program.

Vasocontractile response of aortic rings to KCL and PE was similar in both groups suggesting that the aortic contractile activity is not influenced by sinqularization. Contrary to endothelium-dependent vasodilation, the vasodilation to the NO-donor SNAP showed identical values in moving and sedentary mice. These data suggest that an impairment of the NO/cGMP-pathway is most likely not involved in endothelial dysfunction induced by a sedentary lifestyle in mice.

Assessment of aortic eNOS protein expression showed a significant reduction in sedentary mice. Thus, the overall halved expression of eNOS contributes to the impairment of endothelium-dependent vasodilation induced by physical inactivity. Overall, there was a strong and time-dependent increase of eNOS-protein expression in aotra after 8 and 15 days of exercise training and the similar increase, but as expected to the lesser degree in left ventricular myocardium. In striking contrast, aortic eNOS protein expression did not change after 15 days of exercise in moving mice.

Discussion

Endothelial dysfunction is a well known pathologic condition which is associated with a variety of cardiovascular diseases such as coronary artery disease, hypertension, heart failure and diabetes. The mechanism of endo-

thelial dysfunction is multifactorial and most likely depends on the underlying pathologic process. Here we describe for the first time the development of endothelial dysfunction in healthy young mice with no signs of vascular inflammation or oxidative stress which had been subjected to forced physical inactivity. At the same time, the protein expression of endothelial nitric oxide synthase was reduced by half, while activation of the NO/cGMP pathway by an NO-donor was equally effective in sedentary and moving mice. Therefore, downregulation of eNOS expression appears to be a key mechanism underlying the impairment of endothelial function in young healthy sedentary mice.

Many different conditions, endogenous mediators and drugs have been shown to modulate the expression of eNOS. Among these, mechanisms modifying eNOS expression in response to exercise might be particularly important, since it seems conceivable that a reversion of these mechanisms occur in sedentary mice. Recent reports suggest that there are at least two different mechanisms underlying the upregulation of eNOS expression by exercise. First, exercise increases vascular shear stress which has been shown to increase vascular eNOS expression. Thus, a decreased intensity of physiological shear stress, as expected in sedentary mice, might diminish vascular eNOS expression. Secondly, exercise causes oxidative stress and induce expression of ecSOD, which reduces the vascular O_2^- /H_2O_2 ratio and thus improves NO bioavalability Hydrogen peroxide can increase the expression and activity of eNOS. By generating transgenic mice with an endothelial specific overexpression of catalase we have recently provided evidence that hydrogen peroxide contributes to exercise-induced upregulation of eNOS. In these transgenic mice, 3 weeks of exercise performed according to the protocol used in the present study had no effect on vascular eNOS expression [1].

Our data suggest that unfavorable change of vascular function can be prevented or remarkably delayed in young individuals by either a daily short lasting high intensity training period or a continuous low intensity physical activity. Based on our observations, we propose that regular physical activity may exert beneficial effects in two different ways. In cardiovascular disease patients exercise reduces the degree of endothelial dysfunction, while in young healthy individuals normal physical activity and/or moderate exercise might delay the development of cardiovascular disorders by maintaining normal endothelial function.

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