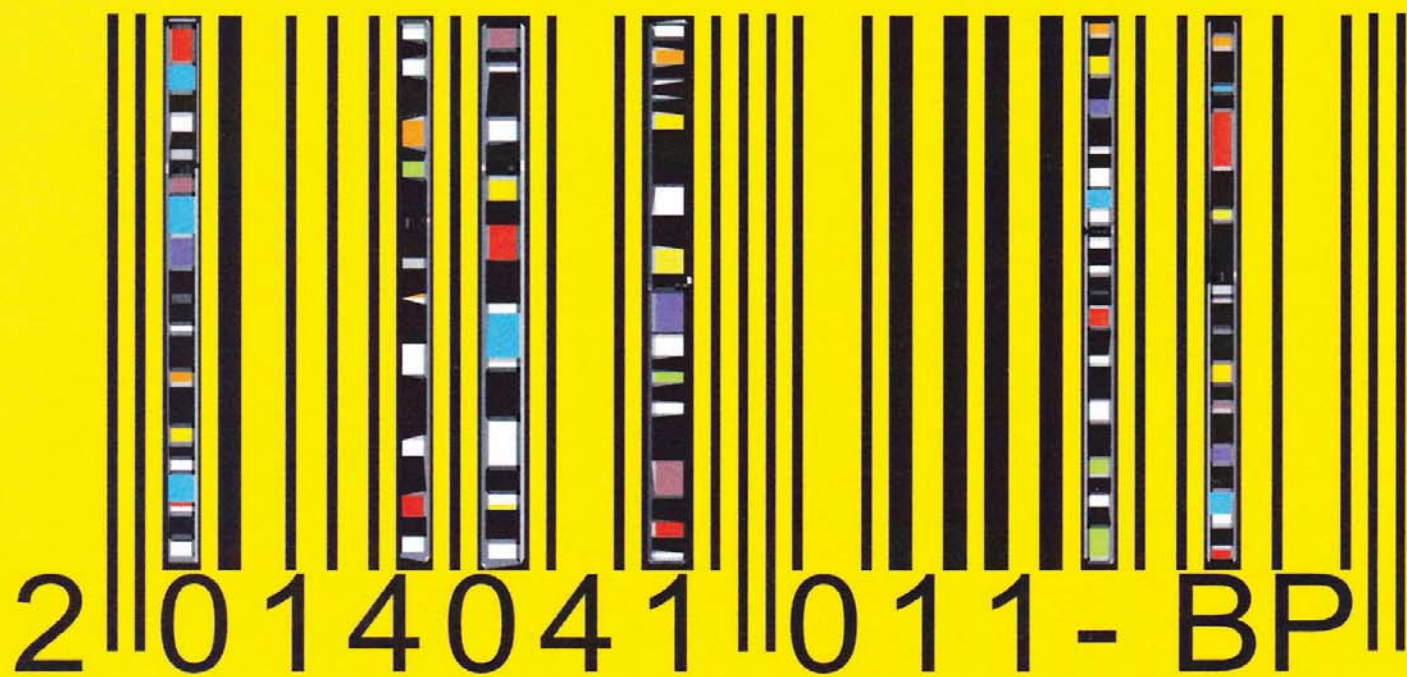




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E/II-9

DEVELOPMENT AND COMPLETE MORPHOLOGICAL AND FUNCTIONAL REVERSIBILITY OF ATHLETE'S HEART IN A RAT MODEL

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Background: Long-term exercise training is associated with characteristic structural and functional cardiac adaptation termed athlete's heart. However the effect of discontinuation of the training (detraining) on left ventricular (LV) function is unclear. Our aim was to evaluate the development characteristics of athlete's heart and the reversibility of morphological and functional changes during detraining.

Methods: Rats were divided into trained (n=15) and control (n=17) groups. Trained rats swam 200 min/day for 12 weeks. Detrained rats remained sedentary for 8 weeks after completion of the training protocol. We regularly performed echocardiographic measurements to investigate the development and regression of exercise-induced cardiac changes. LV pressure-volume analysis was performed to calculate cardiac functional parameters. LV samples were harvested for histological examination and myocardial gene expression analysis was performed using qRT-PCR.

Results: Echocardiographic examinations showed rapidly developing LV hypertrophy in the trained group according to wall thickness values. This adaptation regressed after detraining, which was confirmed by post-mortem measured heart weight and histological morphometry. Unchanged myocardial expression of TGF- β and β -MHC and unaltered amount of LV collagen confirmed the physiologic nature of the observed cardiac hypertrophy. Hemodynamic measurements indicated decreased LV end-systolic volume (LVESV) along with increased stroke volume (SV), improved systolic function (ejection fraction) and contractility (end-systolic pressure-volume relationship), ameliorated active relaxation and mechanoenergetics (mechanical efficiency, ventriculo-arterial coupling) after long-term exercise training. After the detraining period regression of exercise-induced cardiac functional changes were observed: LVESV, SV, LV contractility, active relaxation and mechanoenergetic enhancement reverted completely to control values. Training and detraining did not affect myocardial stiffness.

Conclusions: Our results confirm that the morphological and functional adaptation of exercise-induced physiologic LV hypertrophy completely regressed after 8 weeks of detraining.

Doctoral School: Basic Medicine

Program: Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases

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E/II-10**PHARMACOLOGICAL ACTIVATION OF THE SOLUBLE GUANYLATE CYCLASE INHIBITS PRESSURE OVERLOAD-INDUCED CARDIAC HYPERTROPHY**

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Pathological cardiac hypertrophy is observed in pressure overload of the left ventricle. Elevated intracellular cGMP-levels have been reported to prevent the development of pathological myocardial hypertrophy. We investigated the effects of chronic activation of the cGMP producing enzyme, soluble guanylate cyclase (sGC) by cinaciguat in a rat model of pressure overload-induced cardiac hypertrophy.

We performed aortic banding (AB) to evoke pressure overload-induced cardiac hypertrophy in our rats. Sham operated animals served as controls. Experimental and control groups were treated with 10 mg/kg/day cinaciguat (Cin) or placebo (Co) p.o., respectively. Development of cardiac hypertrophy was investigated by echocardiography. We performed left ventricular (LV) pressure-volume analysis with a pressure-conductance microcatheter to assess cardiac function. In addition to our functional experiments, histological and molecular biological measurements were carried out.

Echocardiography showed marked myocardial hypertrophy in the AB-Co group (left ventricular mass index (LVMI): 3.15 ± 0.09 AB-Co vs. 2.13 ± 0.04 g/ttkg Sham-Co) which was verified by post mortem investigation of the hearts (heart weight/tibial length ratio (HW/TL): 0.384 ± 0.015 AB-Co vs. 0.293 ± 0.008 g/cm Sham-Co) and by histology (cardiomyocyte diameter (CD): 17.37 ± 0.04 AB-Co vs. 14.55 ± 0.12 μm Sham-Co). Increased left ventricular dimensions (left ventricular end-diastolic volume: 414 ± 19 AB-Co vs. 341 ± 19 μl Sham-Co) were observed while ejection fraction and fractional shortening remained unchanged. Cinaciguat did not alter blood pressure (182.27 ± 7.86 AB-Co vs. 174.63 ± 4.53 mmHg AB-Cin, $p = n.s.$) but effectively attenuated left ventricular hypertrophy (LVMI: 2.64 ± 0.06 g/ttkg, HW/TL: 0.339 ± 0.009 g/cm, CD: 15.08 ± 0.10 μm, $p < 0.05$ vs. AB-Co).

Our results demonstrate that chronic stimulation of the NO-cGMP signaling pathway by pharmacological activation of the soluble guanylate cyclase might be a novel therapeutic approach in the prevention of pathological myocardial hypertrophy.

Doctoral School: Basic Medicine

Program: Cardiovascular disorders, Physiology and medicine of ischemic circulatory diseases

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E/II-11

CINACIGUAT PREVENTS DIABETES MELLITUS RELATED CARDIAC ALTERATIONS IN RATS

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Diabetes mellitus (DM) is associated with severely impaired nitric oxide (NO) signalling which leads to development of diabetic cardiomyopathy. Improvement of NO – cGMP signalling have been reported to have cardioprotective effects. We investigated the effects of chronic activation of soluble guanylate cyclase (sGC) by cinaciguat in diabetic cardiomyopathy in a rat model of type-1 DM.

Methods: DM was induced by a single i.p. injection of streptozotocin in our rats. Rats were treated with 10 mg/kg/day cinaciguat (treatment groups) or with placebo (control groups) orally for 8 weeks. Left ventricular (LV) function was assessed using a pressure-volume (PV) conductance microcatheter system. Additionally to our functional experiments, gene expression (by qRT-PCR) and protein expression analysis (by Western blotting (WB)) were performed. Apoptosis was investigated by TUNEL assay. Cardiac remodelling and fibrosis were examined by histology and immunohistochemistry.

Results: DM was associated with significantly elevated endothelial nitric oxide synthase myocardial expressions while WB proved elevated phosphodiesterase-5 and protein kinase G levels (PKG) and decreased PKG activity (p-VASP/VASP ratio). We observed increased atrial natriuretic factor, transforming growth factor- β and matrix metalloproteinase-9 levels and fibrotic remodelling of the diabetic hearts. TUNEL assay showed increased apoptosis in DM. Impaired LV contractility (preload recruitable stroke work (PRSW): 49.5 ± 3.3 vs. 83.0 ± 5.5 mmHg, $p < 0.05$) and diastolic function (time constant of LV pressure decay (τ): 17.3 ± 0.8 vs. 10.3 ± 0.3 msec, $p < 0.05$) were found in the untreated DM group. Cinaciguat treatment prevented DM associated molecular changes and cardiac remodelling and significantly improved systolic (PRSW: 66.8 ± 3.6 vs. 49.5 ± 3.3 mmHg, $p < 0.05$) and diastolic function (τ : 14.9 ± 0.6 vs. 17.3 ± 0.8 msec, $p < 0.05$) compared to untreated DM. It had no effect in non-diabetic control animals.

Conclusions: Our results demonstrate that cinaciguat prevents myocardial alterations and improves cardiac dysfunction in diabetic rats. Pharmacological activation of sGC might be a novel therapeutic approach for diabetic cardiomyopathy. (Supported by the grant OTKA PD100245)

Doctoral School: Basic Medicine

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