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SZÉCHENYI PLAN

Cinaciguat prevents diabetes mellitus related cardiac alterations in rats

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Diabetes mellitus (DM) is associated with impaired nitric oxide (NO)-cGMP signalling which contributes to development of diabetic cardiomyopathy. We investigated whether chronic activation of soluble guanylyl cyclase (sGC) by cinaciguat could be cardioprotective in diabetic cardiomyopathy in rats.

Streptozotocin was used to induce type-1 DM. Rats were treated with 10 mg/kg/day cinaciguat (treatment groups) or with vehicle (control groups) for 8 weeks p.o. Left ventricular (LV) function was assessed using a pressure-volume conductance microcatheter system. Additionally, myocardial gene (qRT-PCR) and protein expression analysis (Western blot (WB)) were performed. Apoptosis was investigated by TUNEL assay. Cardiac remodelling and fibrosis were examined by histology.

Endothelial NO synthase expressions decreased while WB proved elevated phosphodiesterase-5 and protein kinase G levels (PKG) and reduced PKG activity in DM. We observed increased atrial natriuretic factor, transforming growth factor- β , matrix metalloproteinase-9 levels and cardiac fibrosis in untreated DM. TUNEL showed enhanced 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 ms, $p < 0.05$) were found in untreated DM. Cinaciguat prevented DM related molecular changes and cardiac remodelling and 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 ms, $p < 0.05$) compared to untreated DM. It had no effect in non-diabetic rats.

Cinaciguat prevents myocardial alterations and improves cardiac function in diabetic rats. Pharmacological activation of sGC might be a novel therapy for diabetic cardiomyopathy. (Supported by OTKA PD100245)

THIS IS TO CERTIFY THAT

Csaba Mátyás

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