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Striatin signaling in diabetic cardiomyopathy : a novel therapeutic target ?

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Background and aims: Diabetic cardiomyopathy (DCM) is a diabetes mellitus-induced pathophysiological condition that can result in heart failure. Striatin (STRN) is a multivalent protein with dynamic domains including a calmodulin (CaM) binding site. A link between CaM and Protein Kinase A (PKA) is established in diabetes, yet the role of STRN in DCM remains unknown.

Methods: Male Wistar rats were randomly divided into a diabetic group (treated with Streptozotocin-STZ, 60 mg/kg, ip) and a control untreated group (CTRL) for two different time points (8 and 24 weeks post-STZ injection). Serum glucose levels were measured two days post-STZ to confirm diabetic status and one day before killing the rats. Body weights were measured, hearts were rapidly removed and weighed, and proteomics analysis and qPCR were performed in left atrium (LA) and left ventricle (LV) homogenates to assess proteins and mRNA.

Results: STZ induced a 5-fold increase in blood glucose that was maintained at 8W and 24W compared to CTRL rats. Heart weight/body weight ratio was increased at 8W and 24W in diabetic compared to age-matched CTRL rats suggesting cardiac hypertrophy. This

pathological remodeling was further confirmed by increased expression of the mRNA of atrial natriuretic peptide in LV and LA at 8W and 24 W compared to CTRL rats. Protein analysis from diabetic LV showed higher STRN, less myosin heavy chain and higher activity of PKA (p-PKA/PKA ratio) at 8W and 24W post-STZ compared to CTRL rats. Protein analysis revealed that diabetic LA expressed less STRN at 8W and 24W, however the mRNA expression of STRN was found to be increased. PKA was less phosphorylated in the diabetic LAs at 8 W but not significantly altered at 24 W. Interestingly, CaM pull down assay revealed that the interaction between cardiac STRN, p-PKA, and CaM is more pronounced in diabetic LVs than that of CTRL at 24 W post-STZ.

Conclusions: Our data showed that the phosphorylation of PKA paralleled the expression of STRN in the diabetic left hearts. An increased interaction between STRN, p-PKA and CaM in the chronically remodeled diabetic hearts (24W) was observed. Collectively our data support the notion that STRN might be a potential candidate for the long-awaited therapeutic strategies of DCM.