ABSTRACTS

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GLUCAGON-LIKE PEPTIDE-1 PROTECTS AGAINST CARDIAC DYSFUNCTION AND EXTRACELLULAR MATRIX REMODELLING IN EXPERIMENTAL DIABETES

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Glucagon-like peptide-1 (GLP-1) is an insulin-releasing hormone with established cardiovascular actions. Here, we investigated effects of exendin-4, a stable GLP-1 mimetic, on cardiac remodelling in experimental diabetes. Male C57BL/6J mice were injected with streptozotocin (STZ; 50 mg/kg/day for 5 days) or vehicle control prior to starting infusion with exendin-4 (25 nmol/kg/day) at 4 weeks. Continuous treatment with exendin-4 for 8 weeks had no effect on body weight but reduced blood glucose in STZ-treated animals (HbA1c: control 6.6±0.3 vs STZ saline 11.8±1.1, $p<0.01$; exendin-4 9.4±0.9 vs STZ exendin-4 6.5±0.3%, p=NS; n=4–9). Echocardiography indicated that systolic function, assessed by fractional shortening, was similar between groups. However, diastolic dysfunction observed after STZ treatment was attenuated by exendin-4 (mitral valve E/A: STZ saline 1.17±0.04 vs STZ exendin-4 1.51±0.09, $p<0.05$; n=3–8). Interestingly, these functional effects were associated with an improved pro-fibrotic gene expression profile, as assessed by real-time RT-PCR. For example, expression of procollagen I mRNA was reduced in STZ animals after exendin-4 treatment (STZ saline 4.32±0.27 vs STZ exendin-4 3.02±0.37 arbitrary units, $p<0.05$; n=5–8), and similar patterns were observed for procollagen III and fibronectin. Furthermore, differential STZ-induced effects on mRNA expression of matrix metalloproteinase-2 (MMP-2) (control 7.30±0.46 vs STZ saline 9.21±0.49, $p<0.05$; exendin-4 6.50±0.11 vs STZ exendin-4 7.70±0.45 arbitrary units, p=NS; n=5–7) and MMP-9 (STZ saline 1.70±0.35 vs STZ exendin-4 3.84±0.63 arbitrary units, $p<0.05$; n=5–8) were inhibited by exendin-4. These data indicate that GLP-1 protects against adverse cardiac remodelling in diabetes via modulation of the extracellular matrix, although the underlying mechanisms remain unclear.