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C-type natriuretic peptide plays a fundamental role in cardiac function

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Introduction: C-type natriuretic peptide (CNP) is synthesised and released by the endothelium and plays a vital role in the maintenance of vascular homeostasis (Moyes et al. 2014. J. Clin. Invest. 124:4039). However, a similar regulatory role of endogenous CNP in the heart has yet to be elucidated. Therefore, we generated two unique mouse strains (C57BLK6 background) with endothelium (Tie^2-Cre) and cardiomyocyte (αMHC-Cre)-restricted deletion of CNP to investigate if the peptide modulates coronary vascular reactivity and cardiac function.

Method: Langendorff isolated hearts were used to investigate the effect of CNP deletion on coronary vascular reactivity in response to the endothelium-dependent vasodilators bradykinin (10nmol), acetylcholine (0.1-1nmol), and reactive hyperaemia (80s flow cessation). Ischaemia-reperfusion (I/R) injury (35mins ischaemia followed by 60mins reperfusion) was also investigated in cell-specific knockout animals. Pressure overload-induced heart failure (abdominal aortic constriction [AAC]; 6 weeks) was used to study the effect of CNP deletion during cardiac stress. Echocardiography was performed before and after AAC and fibrosis determined by picrosirius red staining. A subset of experiments were repeated in mice with global deletion of natriuretic peptide receptor-C (NPR-C) to delineate the signalling pathway triggered by CNP. Data are presented as mean±SEM and statistical analyses were performed using unpaired Student's t-test, or one- or two-way ANOVA with Bonferroni post-hoc tests.

Results: Coronary endothelial reactivity was reduced in endothelial CNP knockout (ecCNP KO) mice compared to wildtype (WT) in response to bradykinin (21.14±2.89% vs 31.68±2.68%; $P<0.05$; n=7-9), acetylcholine (23.62±6.08% vs 39.84±5.36%; $P<0.05$; n=7-9) and reactive hyperaemia (1493±280.8a.u vs 2804±456.6a.u; $P<0.05$; n=6-8). These observations were paralleled in NPR-C KO animals. ecCNP KO did not exacerbate I/R injury, whilst mice with cardiomyocyte-restricted deletion of CNP (cmCNP KO) and NPR-C KO animals exhibited a larger infarct size compared to WT (cmCNP KO 35.89±3.64% vs 13.02±1.70%; $P<0.0005$; n=8-12; NPR-C KO 35.21±4.46% vs 18.20±4.35%; $P<0.05$; n=7-8). cmCNP KO mice also displayed greater cardiac dysfunction and fibrosis after AAC compared to WT (ejection fraction (EF), 50.35±2.32% vs 64.72±0.81%; fibrosis, 4.14±0.35% vs 2.94±0.35%; both $P<0.05$; n=9-10); similar results were observed in NPR-C KO animals. Infusion of CNP (0.2mg/kg/day; osmotic minipump, s.c.) in WT, but not NPR-C KO, animals rescued the decline in cardiac function.

Conclusions: Endothelial and cardiomyocyte-derived CNP have distinct, complementary roles in the heart, modulating cardiac function by influencing coronary vascular tone and protecting against heart failure and I/R injury. These protective effects of CNP are mediated, at least in part, via NPR-C.