RESEARCH REPORT *PROJECT GRANT #07/04*

Project Title: Effect of chronic Urocortin 2 (Ucn2) treatment following experimental myocardial infarction.

Principle Investigor: Dr Leigh Ellmers

Aims:

- To investigate the physiological and molecular effects of chronic Ucn2 administration in an experimental model of myocardial infarction (MI).
- To provide new insights into the potential therapeutic effects of Ucn2 following ischaemic cardiac injury post MI.

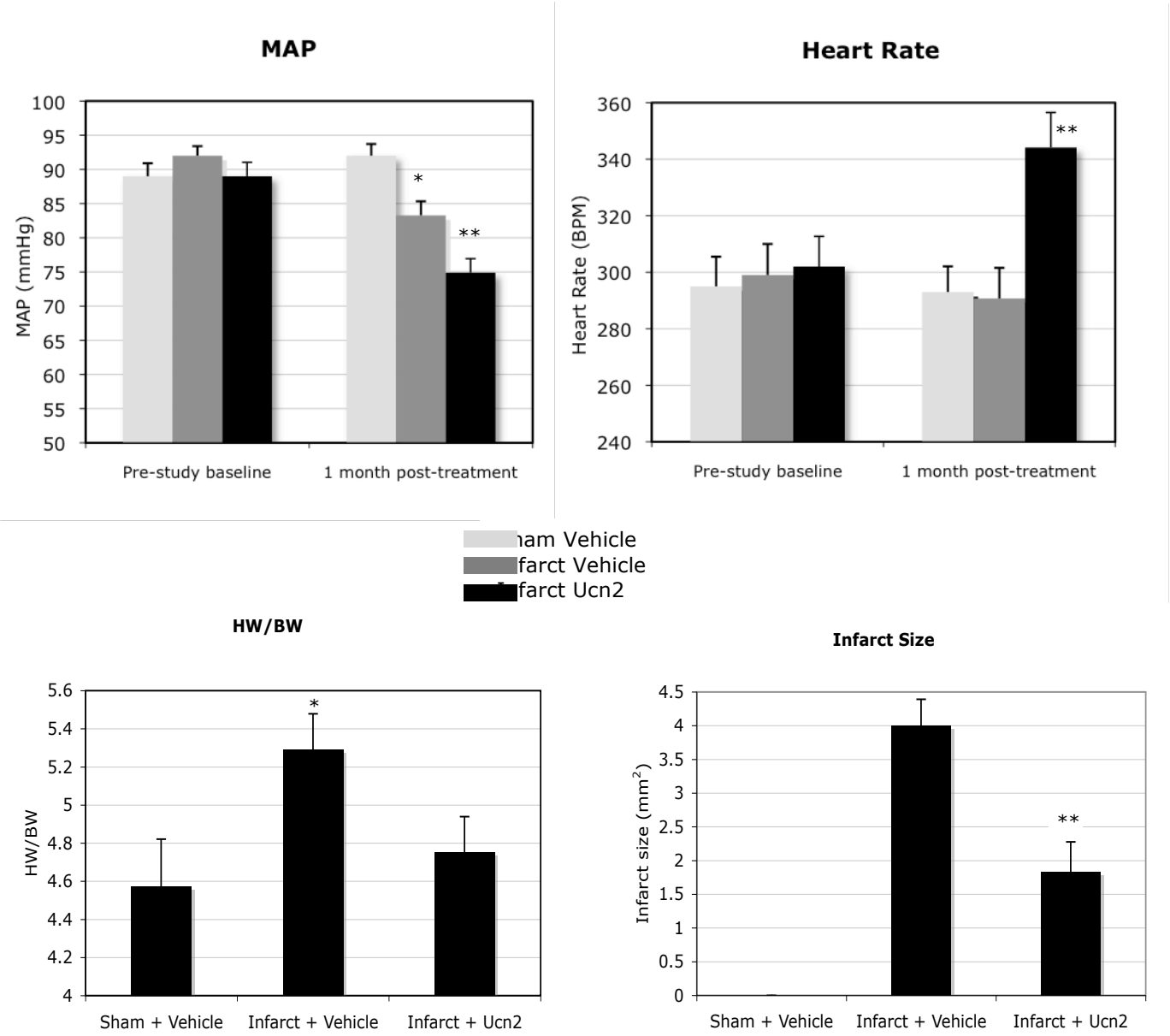
Progress to date:

This project is completed. Two manuscripts have been submitted for publication, and are currently under review (submitted to Circulation Research – Heart Failure).

Results:

Data analysis from the experimental groups, Sham + Vehicle , Infarct + Vehicle and Infarct + Ucn2, indicate Ucn2 treatment post-infarction significantly reduced mean arterial pressure (MAP) when compared to animals post-infarction receiving vehicle control (74±2 versus 83±2 mmHg, $p<0.01$). Heart rate (BPM; beats per minute) was significantly increased in infarcted animals receiving Ucn2 compared to those receiving vehicle (344±12 versus 290±10 BPM, $p<0.01$). Heart weight to body weight (HW/BW), a measure of cardiac hypertrophy, was increased as a result of myocardial infarction (4.57±0.25 versus 5.29±0.18 , $p<0.01$), and was reduced in infarcted animals receiving Ucn2 compared to those receiving vehicle (4.75±0.19 versus 5.29±0.18, $p=0.06$) to control (sham + vehicle) levels. Ucn2 treatment post infarction also significantly reduced infarct size (1.83±0.44 versus 4±0.39 mm^2, $p<0.1$). This data to date suggests Ucn2 has a protective role in the heart after myocardial infarction - reducing cardiac mass and the size of the resulting infarct in the left ventricle (Figure 1).

Figure 1



*p<0.01 Infarct Vehicle vs Sham Vehicle post-treatment

**p<0.01 Infarct Ucn2 vs Infarct Vehicle post treatment

The cardioprotective role of Ucn2 post myocardial infarction is further supported by echocardiography data collected in this study (Table 1). Ucn 2 treatment significantly reduced left ventricle internal diameter (LVID) at both systole and diastole, as well as end systolic volume (ESV). Highly significant reductions in both fractional shortening (FS) and ejection fraction (EF) were observed with Ucn 2 treatment post myocardial infarction.

Echocardiography Parameters	Groups	Pre-study	End of study
LVPWs (mm)	Sham + Vehicle	0.893±0.032	0.917±0.046
	Infarct + Vehicle	1.330±0.021	0.970±0.030
	Infarct + Ucn 2	0.894±0.023	0.874±0.030
LVPWd (mm)	Sham + Vehicle	0.841±0.009	0.924±0.044
	Infarct + Vehicle	0.960±0.006	0.865±0.029
	Infarct + Ucn 2	0.820±0.005	0.832±0.029
IVSs (mm)	Sham + Vehicle	0.698±0.010	0.890±0.026
	Infarct + Vehicle	0.900±0.007	0.850±0.017
	Infarct + Ucn 2	0.917±0.009	0.930±0.018 **
IVSd (mm)	Sham + Vehicle	0.794±0.024	0.859±0.034
	Infarct + Vehicle	0.850±0.015	0.770±0.022 *
	Infarct + Ucn 2	0.834±0.018	0.816±0.022
LVIDs (mm)	Sham + Vehicle	2.148±0.118	1.914±0.136
	Infarct + Vehicle	2.180±.0.078	3.455±0.089 *
	Infarct + Ucn 2	2.465±0.095	2.607±0.091 **
LVIDd (mm)	Sham + Vehicle	3.179±0.107	3.143±0.156
	Infarct + Vehicle	3.450±0.070	4.248±0.102 *
	Infarct + Ucn 2	3.556±0.060	3.778±0.090 **
ESV (ml)	Sham + Vehicle	0.028±0.005	0.019±0.009
	Infarct + Vehicle	0.028±0.003	0.106±0.006 *
	Infarct + Ucn 2	0.034±0.005	0.059±0.007 **
EDV (ml)	Sham + Vehicle	0.090±0.009	0.135±0.027
	Infarct + Vehicle	0.105±0.006	0.192±0.018
	Infarct + Ucn 2	0.115±0.008	0.142±0.020
IVS/LVPW	Sham + Vehicle	0.913±0.031	0.955±0.019
	Infarct + Vehicle	0.885±0.020	0.909±0.013
	Infarct + Ucn 2	0.997±0.022	0.901±0.016
FS (%)	Sham + Vehicle	33.163±1.306	38.208±0.826
	Infarct + Vehicle	36.800±0.855	18.400±0.541 *
	Infarct + Ucn 2	33.041±0.800	30.543±0.538 **
EF (%)	Sham + Vehicle	68.542±1.846	75.608±1.219
	Infarct + Vehicle	73.300±1.208	43.550±0.798 *
	Infarct + Ucn 2	68.853±1.500	65.170±0.850 **

* $p<0.001$ Infarct Vehicle End of Study versus Sham Vehicle End of Study

** $p<0.001$ Infarct Ucn 2 End of Study versus Infarct Vehicle End of Study

Studies to examine the molecular effects of Ucn2 on the heart post myocardial infarction have been performed. SABioscience superarrays were used to determine the expression levels of 45 genes of interest involved in cardiac remodelling and Ucn 2 signalling pathways. Ucn 2 treatment significantly down regulated genes involved in transforming growth factor beta signalling pathways, deleterious pathways involved in the activation of the renin-angiotensin system which is involved in controlling fibrotic or scarring pathways in the heart.

Significance:

Cardiovascular disease is a leading cause of death and disability in New Zealanders. Exploration of potential new treatments is therefore crucial. Advances to date in the treatment of heart disease have focussed on the understanding and manipulation of a number of hormone systems involved in heart disease. The novel peptides Ucn1, Ucn2 and Ucn3 have been shown to produce beneficial short-term cardiovascular, hormonal and renal effects in experimental heart failure. In this study we have investigated the role of Ucn2, one of the most promising members of the urocortin family as a possible therapeutic agent, by chronically administering this hormone after myocardial infarction in mice. Our results have demonstrated numerous cardioprotective properties of Ucn2. Treatment with this peptide for 4 weeks post myocardial infarction reduced cardiac mass to pre-infarction levels and significantly reduced infarct size and blood pressure, all beneficial actions after a heart attack. In addition, cardiac function was significantly improved after myocardial infarction in mice treated with Ucn2. Urocortin 2 also down-regulated deleterious signalling pathways involved in cardiac remodelling at the molecular level. This study highlights the beneficial long-term cardioprotective effect of Ucn2 post myocardial infarction.

LAY RESEARCH REPORT

Cardiovascular disease is a leading cause of death in New Zealanders. Despite advances in therapy, the prognosis remains poor for those effected, necessitating investigation of possible new treatments. The Urocortin family of hormones may have beneficial effects in heart disease. In this study we investigated the role of urocortin 2 as a possible therapeutic agent. We administered this hormone after heart attack in mice to assess its function in ameliorating the damage associated with this type of heart disease. Our study has shown urocortin 2 is a cardioprotective hormone which reduces the damage to the heart after a heart attack and helps the maintain normal cardiac function.