NEGATIVE MYOCARDIAL EFFECTS OF CYCLIC GMP ARE ENHANCED IN OBESE RATS

James Tse PhD, MD, Harvey R. Weiss PhD, Elizabeth Katz, MS, and Peter M. Scholz MD

Departments of Anesthesia, Physiology & Biophysics and Surgery, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ 08901, USA

INTRODUCTION: It has been shown that lack of leptin, a regulator of food intake or leptin resistance lead to obesity¹. In leptin defiant mice, functional decrements in isolated ventricular myocytes caused by cyclic GMP (cGMP) are greatly increased². We tested the hypothesis that the negative myocardial responses to cGMP would be enhanced in leptin-resistant obese rats.

METHODS: Experiments were performed in anesthetized open chest 16 male Zucker obese rats and 13 age-matched control rats after ICACUC approval. Arterial blood gases, heart rates and blood pressures were obtained after stabilization and 15 min after applying either vehicle (saline) or 8-Br-cGMP (1 mM) topically to the left ventricular surface. Coronary blood flow (¹⁴¹Ce-labeled microspheres) and O₂ extraction (microspectrophotometry) measurements were used to determined myocardial O₂ consumption (VO₂). Protein phosphorylation by cGMP protein kinase (protein electrophoresis) and low Km cAMP phosphodiesterase (A-PDE) (total and cGMP-inhibited) activities were also determined. ANOVA was used for statistical analysis. A value of p<0.05 was accepted as significant. Data were presented as Mean±S.E.M.

RESULTS: The body weights (g) of the Zucker obese rats were greater than their age-matched controls (523±17 vs. 322±12) and their heart weights (g) were also greater (1.24±0.05 vs. 1.06±0.03). The obese rats had higher basal systolic BP (mmHg) than the controls (129±7 vs. 95±8). 8-Br-cGMP significantly reduced cardiac output (ml/min) in the obese rat (296±71 to 168±25) but not in the controls (228±41 to 207±30). 8-Br-cGMP also significantly reduced myocardial VO₂ (ml O₂/min/100g) in the obese rats (54±9 to 35±6) but not in the controls (53±13 to 45±7). There were no differences in the pattern of basal or cGMP-stimulated protein phosphorylations or total A-PDE activities between the two groups. However, addition of cGMP significantly inhibited A-PDE activities in the control rats (-30±4%) but not in the obese rats (-15±12%).

DISCUSSION: The data showed that the cGMP-induced negative myocardial effects were enhanced in leptin-resistant obese rats. This could be caused by a decrease in myocardial cGMP-inhibited A-PDE activities in the obese rats.

REFERENCES: 1. Curr Opin Nephrol Hypertens 13:215-23, 2004. 2. Am J Physiol 285: H2111-7, 2003.