Rescue of LPS-induced Left Ventricular Dysfunction by Intralipid is Mediated by Phosphorylation of STAT3

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INTRODUCTION

Sepsis-induced cardiomyopathy contributes to significant mortality and morbidity. Despite decades of research delineating molecular pathways and mediators leading to the manifestation of myocardial dysfunction in sepsis, a dearth of novel therapeutic targets still remains. Intralipid (ILP) has been demonstrated in animal models and humans to mitigate the cardio-depressant effects of local anesthetics and I/R injury, possibly *via* restoration of metabolic dysfunction, activation of cardio-protective signaling and augmentation of contractility. However, its potential role in sepsis-induced cardiac dysfunction has yet to be elucidated. In this study, we examine whether ILP improves left ventricular (LV) dysfunction secondary to lipopolysaccharide (LPS)-endotoxemia in rats.

METHODS

Adult female Sprague-Dawley rats (n=8) weighing 250-350g, received a single intraperitoneal injection of LPS (20mg/kg). Echocardiography was performed on the rats at baseline prior to injection of LPS, and then at 6h post-LPS, in order to assess LV ejection fraction (LVEF, %). Under anesthesia, femoral vein was cannulated and rats were randomly divided to receive either 20% ILP (n=4) or phosphate buffered saline (PBS; n=4) as a 5 ml/kg bolus followed by a 0.5 ml/kg/min infusion over 10 min and echocardiography was conducted at 1, 5 and 10 min to reassess LVEF. At 10 min, LV tissue was collected and Western blots were performed to assess for GSK and STAT3 phosphorylation. Values are expressed as mean±SEM. $P<0.05$ is considered statistically significant.

RESULTS

Baseline LVEF in PBS and ILP groups before LPS were 75.7±1.1% and 74.2±1.2% respectively. Six hours after LPS injection, LVEF was significantly decreased (LVEF= 54.3±4.8% in PBS group, and 46.0±2.5% in ILP group; both $p<0.05$ *vs.* baseline). Rats treated with ILP had improved systolic function at 5 min (LVEF=63±3.9% $p<0.05$ *vs.* 6h post LPS) that peaked at 10 min (LVEF=70.5±2.3%, $p<0.05$ *vs.* 6h post LPS). PBS group had no significant improvement in LVEF at 5 and 10 min (LVEF=58.4±6.4%, and 58.9±7.8% respectively; both p=n.s. *vs.* 6h post LPS). Western blots demonstrated increased phosphorylation of STAT3 (~2-fold) in ILP treated rats ($p<0.05$) whereas GSK phosphorylation was unchanged (p=n.s.).

DISCUSSION

LPS-treated rats demonstrate a profound reduction in LV systolic function. Acute administration of ILP significantly improves LV function likely mediated via STAT3 phosphorylation. This rescue effect of ILP suggests a potentially important role for ILP as a novel treatment modality in the setting of sepsis-induced cardiac dysfunction.