ADIPONECTIN RESCUES LIPOTOXIC CARDIOMYOPATHY BY PROMOTING SPHINGOSINE-1-PHOSPHATE AND CERAMIDASE EXPRESSION

Poster Contributions
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Authors: Geoffrey Weiting Cho, Yukiko Miyauchi, Joshua Johnson, William L. Holland, Joseph Hill, UT Southwestern Medical Center, Dallas, TX, USA

Background: Hyperlipidemia and ceramide accumulation are significant factors in cardiovascular disease, contributing to atherosclerosis and lipotoxic cardiomyopathy. The adipose-derived circulating factor adiponectin, as well as sphingosine 1-phosphate (S1P), may function to limit the harmful effects of ectopic lipid deposition in the heart. We previously demonstrated that adiponectin promotes an increase in ceramidase activity leading to ceramide catabolism and S1P generation. Here, we hypothesized that adiponectin can rescue lipotoxic cardiomyopathy by regulation of this ceramide:S1P rheostat.

Methods: We engineered transgenic mice with cardiomyocyte-specific over-expression of LPL-GPI, a model of lipotoxic cardiomyopathy, that additionally harbored a cardiomyocyte-specific adiponectin transgene (alpha-MHC promoter). We also engineered LPL-GPI knockout mice harboring an inactivated gene coding for adiponectin. Ventricular size and function were assessed noninvasively by echocardiography at 15 weeks of age.

Results: Over-expression of adiponectin improved ventricular systolic function (fractional shortening) by 20.1% (±10.4%, n=9, p<0.05 vs LPL-GPI control). LVID decreased 30.6% (±7.6%, n=9, p<0.05). Adiponectin over-expression was associated with reduction in ceramide and hexosylceramide levels by 33.4% and 40.6%, respectively (±10.2, n=6, p<0.05; ±6.3, n=6, P<0.005 both vs LPL-control), and a 36.6% (±13.3%, n=3, p<0.05 vs LPL-control) increase in S1P levels. These changes were associated with robust rescue of cardiovascular mortality at 15 months (60%, n=12, p<0.01). These cardioprotective effects were not seen in adiponectin knockouts.

Conclusion: Adiponectin inhibits cardiac ceramide accumulation, promotes S1P formation, rescues cardiac function, and improves cardiovascular mortality in a model of lipotoxic cardiomyopathy. Together, these data suggest that manipulation of adiponectin is a novel means of treating lipotoxic heart disease.