

Leucine Amplifies the Effects of Metformin on Insulin Sensitivity and Glycemic Control in Diet-induced Obese Mice

Session Sunday General Poster Session

General Poster Sessions

Number 1108-P | Sunday, June 15, 2014 at 12:00 PM – 2:00 PM | Location: Poster Hall (Hall D-North)

Category Clinical Therapeutics/New Technology–Oral Agents

Author(s) BINGZHONG XUE, LIZHI FU, FENFEN LI, ANTJE BRUCKBAUER, QIANG CAO, XIN CUI, RUI WU, MICHAEL B. ZEMEL, HANG SHI, *Atlanta, GA, Knoxville, TN*

We previously found leucine to activate Sirt1 and to potentiate other activators of the sirtuin/AMPK pathway, including resveratrol, resulting in improvement of insulin sensitivity. Since metformin also converges on this pathway, we first demonstrated marked synergy between leucine and metformin on Sirt1, AMPK and insulin sensitivity in myotubes and adipocytes. In vivo effects on glycemic control were then tested in a mouse model of high fat diet induced insulin resistance. High fat diet (HFD) for 6 weeks induced pronounced fasting and post-prandial hyperglycemia and hyperinsulinemia which were not significantly affected by the addition of leucine (Leu, 24 g/kg diet) with or without resveratrol (Res, 12.5 mg/kg diet). However, adding sub-therapeutic levels of metformin (Met) that exert no independent effects (0.05 - 0.25 g/kg diet) to Leu-Res resulted in dose-responsive reductions in fasting and post-prandial glucose ($p < 0.01$) which were evident within 7 days of treatment and sustained for six weeks until sacrifice. Met (0.25 g/kg)-Res-Leu produced a comparable reduction in fasting glucose (30 mg/dL) to a standard therapeutic Met dose (1.5 g/kg diet; ~300 mg/kg BW), as well as comparable glucose response to an insulin tolerance test and a significantly greater reduction in area under the curve (AUC) in glucose tolerance tests (GTT) ($p < 0.0001$). This study was then repeated without resveratrol, with comparable results. Leu-Met (0.25 g/kg) reduced blood glucose levels by 30 mg/dL ($p < 0.001$), and the area under the GTT curve by 16% ($p < 0.001$), similar to effects of therapeutic levels of Met (1.5 g/kg), while the Leu-Met (0.5 g/kg diet) resulted in greater improvements in glucose (43 mg/dL) GTT AUC (25%; $p < 0.001$). Thus, adding Leu to Met enables a dose reduction of 66% with improved efficacy and of 83% with comparable efficacy to standard metformin, and resveratrol is not a necessary component for this synergy.

Keywords Leucine and metaformin synergy, Sirt1 and AMPK, GLycemic control

American Diabetes Association
1701 North Beauregard Street Alexandria, VA 22311

