Diabetes 2014; 63 (Suppl 1):A463

American Diabetes Association 74th Scientific Sessions | June 13-17, 2014 | San Francisco, CA

Synergy between Metformin and Leucine in Sirtuin Signaling and Fat Oxidation In Vitro, and in Reducing Lipid Accumulation in Diet-induced Obese Mice

Session Monday General Poster Session

General Poster Sessions
Number 1797-P | Monday, June 16, 2014 at 12:00 PM – 2:00 PM | Location: Poster Hall (Hall D-North)
Category Integrated Physiology–Liver

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We previously found leucine (Leu) to stimulate Sirt1 and AMPK signaling in vitro and in vivo. Since metformin (Met) converges on the same pathway, we have tested the ability of Leu to amplify the effects of Met on AMPK, Sirt1 and lipid metabolism. Met (10-100 μM) and Leu (0.5 mM) combinations synergistically increased AMPK phosphorylation and activity 50% ($p<0.01$), Sirt1 activity 40-60% ($p<0.01$), mitochondrial mass 24-51% ($p<0.04$) and fatty acid oxidation (FAO) by 50-110% ($p<0.01$) in adipocytes and myotubes and the effects on AMPK and FAO were augmented by low-dose (200 nM) resveratrol (Resv). To evaluate this synergy in vivo, diet-induced obese (DIO; induced by high fat diet) mice were fed high Leu (24 g/kg diet) with or without Resv (12.5 mg/kg diet) with or without subtherapeutic levels of Met (0.05-0.50 g/kg diet) or therapeutic levels of Met (1.5 g/kg diet; ~300 mg/kg BW). Compared to control low-fat diet mice, DIO mice exhibited a 10-fold increase in inguinal fat pad weight and 69% increase in liver weight ($p<0.0002$); histology confirmed the latter to be due to steatosis. Neither Leu nor Resv, individually or in combination, affected fat pad or liver mass in the absence of Met. However, addition of subtherapeutic Met reduced fat pad mass by 31%, comparable to the effets of therapeutic Met ($p<0.0001$). Moreover, addition of subtherapeutic levels of Met resulted in a dose-responsive decrease in liver mass, with the highest dose exerting significantly greater effects than therapeutic levels of Met and fully reversing hepatic steatosis ($p<0.0002$). This was accompanied by substantial reversal of DIO-induced inflammation as measured by serum CRP ($p<0.001$). Thus, Leu and Met exhibit significant synergy with respect to Sirt1-AMPK signaling, and a low-dose Leu-Met combination exerts comparable effects on adiposity to therapeutic doses of Met and fully reverses hepatic steatosis in DIO mice, enabling 66-83% Met dose reduction in this model.

Keywords Leucine and metformin synergy, Sirt1 and AMPK, lipid metabolism

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