Leucine-Metformin Synergy Activates the AMPK/Sirt1 Pathway to Increase Insulin Sensitivity in Skeletal Muscle and Glucose and Lipid Metabolism and Lifespan in C. elegans

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Introduction
AMPK and Sirt1 are key sensors of energy status and regulators of glucose and lipid metabolism. While insulin resistance and diabetes are associated with impairment of this pathway, the AMPK-Sirt1 axis improves hyperglycemia and insulin sensitivity associated with increased inflammation in visceral adipose tissue and with whole-body glucose and fat utilization in C. elegans, and increased median and maximal lifespan.

Materials and Methods

Cell culture
C2C12 myotubes were maintained in DMEM containing 2% horse serum and 1% Pen-Strep for 5 days, then treated with indicated treatments.

Western Blot

Met-Leu treatment for 2 hours, then 20 min insulin (10 nM) stimulation.

Cell-free Sirt1 activity:

C. elegans:
Indicated treatments synergistically activate Sirt1 at low NAD concentrations (typical of energy replete states), resulting in improvements in energy metabolism and insulin sensitivity.

Results

Conclusions

Low dose metformin (50-100 μM) combined with leucine synergistically activate Sirt1 at low NAD* levels (<100 μM), characteristic of repletes states.

The Met-Leu combination increases insulin-independent glucose disposal in myotubes, associated with an increase in AMPK and IRS phosphorylation.

Met-Leu restored high-glucose induced impaired glucose utilization and fat utilization in C. elegans, and increased median and maximal lifespan.

References