Leucine Synergizes With Phosphodiesterase 5 (PDE5) Inhibitors And Metformin To Reverse Hepatic Lipid Accumulation And Inflammation And Treat Non-alcoholic Fatty Liver Disease (NAFLD)

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Abstract
Leucine treatment in non-alcoholic steatohepatitis (NASH) and liver injury results in a substantial reversal of this phenotype.

Introduction
Sirt1 and AMPK are key regulators of systemic and hepatic lipid and glucose metabolism and inflammatory pathways. High fat diets and diabetes downregulate the Sirt1/AMPK axis, resulting in hepatic steatosis and inflammation, similar to the effects of hepatic Sirt1 knockout, while Sirt1 overexpression or activation protects against non-alcoholic steatohepatitis (NASH) in preclinical models (1-3), thus representing therapeutically targets for NAFLD and NASH (3).

We have demonstrated leucine to allosterically activate Sirt1 (4), and represent therapeutic targets for NAFLD and NASH (3).

Materials & Methods
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Animals: C57BL/6 mice (n=10/group) were fed either a low fat (LF) diet or a high fat/high cholesterol diet (HC) containing 1.25% cholesterol by weight and 45% calories as saturated fat (lard) for 6-8 weeks to induce the development of NAFLD and insulin resistance. Then they were randomized to one of the treatment groups for additional 6-8 weeks.

Treatment groups:

1. Control LF = 10% calories from fat
2. Control HC = 45% calories from fat
3. Palmitate (2.0 g/kg diet) = 60% decrease
4. HC + metformin (25 mg/kg diet) = 60% decrease
5. HC + leucine (24 g/kg diet) = 60% decrease
6. HC + metformin (25 mg/kg diet) + leucine (24 g/kg diet) = 60% decrease

Results

The triple combination of leucine, low dose metformin and low dose sildenafil interacts on the AMPK-Sirt1-eNOS/NO pathway to increase fatty acid oxidation and to reduce lipid accumulation in hepatocytes

Leu-Met-Sild feeding in mouse NASH-model resulted in significant reductions of liver weight, liver triglycerides and ALT, and reversed the diet-induced steatohapeatosis

Conclusions

![Interactive Effects of leucine, metformin and sildenafil in vivo (mice)](image)

References
2. Lin Y, Lin D, Zeng Y, Shi Z. Long-term leucine feeding increases hepatic AMPK activation and lipid content. Metabolism 2015, 64:845-856