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Synergistic Effects of Leucine and β-Hydroxy-β-Methyl- Butyrate (HMB) with Phosphodiesterase (PDE) Inhibitors on Sirtuin Activation

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Abstract

We recently demonstrated leucine and HMB synergy with resveratrol and other polyphenols to activate sirtuin signaling and downstream pathways, including mitochondrial biogenesis and fatty acid oxidation (FAO). Since resveratrol also activates Sirt1 via PDE inhibition with AMPK activation, we determined synergy between leucine or HMB and low-dose PDE inhibitors in stimulating aerobic metabolism in adipocytes and myotubes. PDE inhibitors were studied at concentrations that exerted no independent effects in the systems studied (0.1 – 10 nM); only PDE 5 inhibitors (sildenafil and icariin) exhibited synergy with leucine (0.5 mM) or HMB (5 μM) in stimulating fat oxidation in myotubes (~200%, $p=0.003$) and adipocytes (~100%, $p<0.05$). Both PDE inhibitors exhibited comparable synergy with leucine and HMB in increasing NO production (~50%: $p<0.0003$) and corresponding increases in mitochondrial biogenesis (~15–30%, $p<0.01$). Thus, leucine-dependent Sirt1/AMPK signaling synergizes with PDE 5-regulated cGMP signaling to stimulate mitochondrial biogenesis and aerobic metabolism, resulting in significant effects at concentrations that are ~1% of the therapeutically-effective plasma concentrations of these drugs.