

Mild Mitochondrial Uncoupling in Mice Affects Energy Metabolism, Redox Balance and Longevity

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Calorie restriction is the most effective non-genetic intervention to enhance life span known to date. A major research interest has been the development of therapeutic strategies capable of promoting the beneficial results of this dietary regimen. In this sense, we propose that compounds that decrease the efficiency of energy conversion, such as mitochondrial uncouplers, can be caloric restriction mimetics. Treatment of mice with low doses of the protonophore 2,4-dinitrophenol promotes enhanced tissue respiratory rates, improved serological glucose, triglyceride and insulin levels, decrease of reactive oxygen species levels and tissue DNA and protein oxidation, as well as reduced body weight. Importantly, dinitrophenol-treated animals also presented enhanced longevity. Our results demonstrate that mild mitochondrial uncoupling is a highly effective *in vivo* antioxidant strategy, and describe the first therapeutic intervention capable of effectively reproducing the physiological, metabolic and life span effects of caloric restriction in healthy mammals.

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