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1 - METABOLIC EXPOSURES TO PERIODIC CYCLES OF LIMITED FOOD INTAKE BOOSTS HEALTHSPAN AND DEFINES A MOLECULAR MEMORY OF FASTING

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Resumen

Introduction: Caloric restriction and other forms of fasting, such as cycles of limited food intake, promote healthy aging and prevent age-associated metabolic diseases. Underneath these strategies, identifying biological and nutritional adaptations remains a scientific challenge with social and economic implications.

Methods: Middle-aged mice were subjected for 5 months to 4:10 feeding cycles, consisting of 4 days of very low-calorie intake (VLCI) followed by 10 days of *ad libitum* regime. The impact of 4:10 cycles was determined with respect to whole-body physiology, metabolic and bioenergetic status, as well as the dynamic response to stimuli by metabolite profiling. Hepatic plasticity of the spliceosome was also evaluated.

Results: Short-term benefits of VLCI included body weight, fat and lean mass loss, and up-modulation of 4 hepatic pathways (purines, lipids/ketone bodies, ascorbate, and redox). Long-term benefits of repeated 4:10 cycles included body weight and fat mass loss, enhanced physical performance, and a long-lasting metabolic memory of fasting. Genes of the hepatic splicing machinery classified into 7 independent clusters of unique expression patterns. Interestingly, metabolic exposures to VLCI primed some clusters to have a memory of fasting. A pairwise comparisons between ad libitum *vs.* fasted state further identified a molecular signature of 64 spliceosomal genes strongly altered, the vast majority downregulated [80%]. Of note, some of them correlated with well-known biomarkers of the organismal bioenergetic and nutritional status.

Conclusions: This study supports the concept that organismal, metabolic, and molecular adaptations to periodic cycles of VLCI may be partially driven by a long-lasting nutritional memory, which provide information for the optimization of the use of cycles of limited food intake to promote health.

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