

## Comparative Effects of Resveratrol and Energy Restriction on Liver Fat Accumulation and Hepatic Fatty Acid Oxidation

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**Abstract :** Introduction: Energy restriction is an effective approach in preventing liver steatosis. However, due to social and economic reasons among others, compliance with this treatment protocol is often very poor, especially in the long term. Resveratrol, a natural polyphenolic compound that belongs to stilbene group, has been widely reported to imitate the effects of energy restriction. Objective: To analyze the effects of resveratrol under normoenergetic feeding conditions and under a mild energy restriction on liver fat accumulation and hepatic fatty acid oxidation. Methods: 36 male six-week-old rats were fed a high-fat high-sucrose diet for 6 weeks in order to induce steatosis. Then, rats were divided into four groups and fed a standard diet for 6 additional weeks: control group (C), resveratrol group (RSV, resveratrol 30 mg/kg/d), restricted group (R, 15 % energy restriction) and combined group (RR, 15 % energy restriction and resveratrol 30 mg/kg/d). Liver triacylglycerols (TG) and total cholesterol contents were measured by using commercial kits. Carnitine palmitoyl transferase 1a (CPT 1a) and citrate synthase (CS) activities were measured spectrophotometrically. TFAM (mitochondrial transcription factor A) and peroxisome proliferator-activator receptor alpha (PPAR $\alpha$ ) protein contents, as well as the ratio acetylated peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 $\alpha$ )/Total PGC1 $\alpha$  were analyzed by Western blot. Statistical analysis was performed by using one way ANOVA and Newman-Keuls as post-hoc test. Results: No differences were observed among the four groups regarding liver weight and cholesterol content, but the three treated groups showed reduced TG when compared to the control group, being the restricted groups the ones showing the lowest values (with no differences between them). Higher CPT 1a and CS activities were observed in the groups supplemented with resveratrol (RSV and RR), with no difference between them. The acetylated PGC1 $\alpha$  /total PGC1 $\alpha$  ratio was lower in the treated groups (RSV, R and RR) than in the control group, with no differences among them. As far as TFAM protein expression is concerned, only the RR group reached a higher value. Finally, no changes were observed in PPAR $\alpha$  protein expression. Conclusions: Resveratrol administration is an effective intervention for liver triacylglycerol content reduction, but a mild energy restriction is even more effective. The mechanisms of action of these two strategies are different. Thus resveratrol, but not energy restriction, seems to act by increasing fatty acid oxidation, although mitochondriogenesis seems not to be induced. When both treatments (resveratrol administration and a mild energy restriction) were combined, no additive or synergic effects were appreciated. Acknowledgements: MINECO-FEDER (AGL2015-65719-R), Basque Government (IT-572-13), University of the Basque Country (ELDUNANOTEK UFI11/32), Institut of Health Carlos III (CIBERobn). Iñaki Milton is a fellowship from the Basque Government.

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