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OBESITY

Fasting every other day promotes beiging of white adipose tissue

> …intermittent fasting could be a viable nonpharmacological strategy for treating obesity and related metabolic disorders

New research published in *Cell Metabolism* shows that intermittent fasting can markedly reduce obesity, insulin resistance and hepatic steatosis by selectively promoting the beiging of white adipose tissue (WAT) via modulation of the gut microbiota.

"The induction of beige fat, which results in increased metabolism (that is, the burning of calories), has been proposed for the treatment of obesity and other metabolic diseases, but there are no clinically feasible approaches for activating thermogenic beige fat in humans," explain study team leaders Guolin Li and Frank Gonzalez. "By studying the mechanism by which intermittent fasting decreases obesity and related metabolic diseases in mice, we uncovered a novel role for the gut microbiota in adipose beiging and associated weight loss."

To investigate the metabolic changes induced by intermittent fasting, mice fed a regular-chow diet were subjected to 15 cycles of every-other-day fasting (EODF). Compared with mice that were fed *ad libitum*, EODF mice gained less weight, had reduced WAT mass (in the visceral epididymal depot), noticeable beiging of subcutaneous (inguinal) WAT and both an increased number of multilobular adipocytes (a characteristic of beige adipocytes) and markedly increased *Ucp1* mRNA expression in inguinal WAT. Although increased *Ucp1* expression was evident after just three cycles of EODF, body weight and energy expenditure were unchanged, indicating that WAT beiging precedes EODF-mediated energy expenditure and weight loss.

Next the team investigated whether EODF-induced WAT beiging was dependent on the composition of the gut microbiota. 16S rRNA sequencing of caecum microbiota samples revealed that EODF markedly increased both the abundance of Firmicutes and the Firmicutes to Bacteroidetes ratio (8.9), compared with that in mice fed *ad libitum* (3.4). Transplantation of microbiota from the EODF mice, but not from those fed *ad libitum*, into germ-free mice resulted in pronounced upregulation of *Ucp1* expression in inguinal WAT. Moreover, unlike control mice, those made germ-free by treatment with antibiotics were resistant to EODF-induced WAT beiging, thereby confirming that a shift in the composition of the microbiota is required to induce WAT beiging.


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Finally, the team showed that EODF-induced WAT beiging could suppress obesity and metabolic disease in a mouse model of the metabolic syndrome. Mice with diet-induced obesity (DIO) that were fed a high-fat diet for 3 months, followed by 15 cycles of EODF, had markedly lower body weights, better insulin sensitivity and less hepatic steatosis than their *ad libitum* counterparts. Importantly, suppression of obesity and metabolic disease could be replicated in germ-free mice with DIO that were transplanted with EODF microbiota, thus confirming that the microbiota are sufficient to mediate the beneficial effects of the EODF regimen.

"We found that intermittent fasting dramatically ameliorates obesity, insulin resistance and hepatic steatosis in mice with DIO," remark Li and Gonzalez. "Given that intermittent fasting has been practised by certain religious groups for thousands of years, our findings suggest that intermittent fasting could be a viable nonpharmacological strategy for treating obesity and related metabolic disorders. It should however be emphasized that the role of the gut microbiota and adipose beiging in weight loss associated with intermittent fasting first needs to be directly investigated by clinical trials in humans."

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ORIGINAL ARTICLE Li, G. *et al.* Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2017.08.019 (2017)