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METABOLISM

Metabolic effects of intermeal fasting

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An isocaloric twice-a-day (ITAD) feeding regime induces metabolic improvements in mice by activating autophagy in certain tissues. If validated in human studies, these novel findings could be used to prevent obesity and type 2 diabetes mellitus.

Fasting is known to induce autophagy, which has beneficial effects on lipid metabolism. "Given that autophagy decreases with obesity and/or age, we began to consider the possibility that providing two intervals of fasting in each circadian period would stimulate autophagy that, in turn, could prevent age and/or obesity-associated metabolic decline," explains lead author Rajat Singh. Thus, Singh and colleagues developed the ITAD feeding strategy to model internal fasting and remove scattered feeding.

The researchers split the mice into two groups: those on ITAD feeding were fed at 8:00–10:00 hours and 17:00–19:00 hours and the control mice were fed *ad libitum*. Importantly, both groups received the same amount of calories overall. After 3 months, the two groups of mice were a similar weight; however, ITAD-fed mice had reduced fat mass and increased muscle mass. ITAD feeding also resulted in a range of metabolic benefits, such as improved glucose clearance, reduced hepatic and circulating levels of lipids and increased energy expenditure.

Interestingly, the reduction in fat mass in the ITAD-fed mice was associated with an increase in markers for browning of subcutaneous fat. The researchers also point out that the increase in muscle mass is a unique benefit of ITAD feeding; other regimes, such as calorie restriction, often result in loss of muscle mass. "We are excited about the possibility that ITAD feeding could potentially benefit aged individuals or those with sarcopenia by sustaining muscle mass," says Singh.

To explore the mechanistic contributions of autophagy, the researchers created distinct tissue-specific autophagy-null mice by knocking out *Atg7* in POMC neurons, liver, Myf5 progenitors and adipose tissue. This analysis revealed that autophagy in adipose tissue is required for browning of fat during ITAD feeding, and also for suppression of hepatic gluconeogenesis. Autophagy in POMC neurons and the liver was shown to drive the decrease in circulating and hepatic levels of lipids, while Myf5 autophagy was required for muscle-specific benefits.

"Our studies in mice … suggest that individuals are likely to benefit from a two meals-a-day plan, although the extent of the benefit in humans may depend on genetic make-up, the duration of ITAD feeding, and certainly the age or underlying disease modifiers," concludes Singh. Singh and colleagues are now planning to explore the role of the gut in the beneficial effects of ITAD feeding, and look forward to testing the strategy in humans.

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