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Acute Adaptation of Energy Expenditure Predicts Diet-Induced Weight Loss: Revisiting the Thrifty Phenotype



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Energy expenditure decreases in response to weight loss. Although this phenomenon is likely driven, at least in part, by neuroendocrine adaptations to caloric imbalance, its underlying molecular mechanisms are not yet fully elucidated (1). Because adaptive thermogenesis intensifies and is sustained over time as weight loss increases (2,3), it is considered to mitigate weight loss. The variability of adaptive thermogenesis in response to weight changes has also been suggested to contribute to an individual's relative susceptibility to obesity and associated complications, such as type 2 diabetes. Rooted in a gene-centered view of evolution and natural selection, this notion was coined the “thrifty gene” hypothesis (4). Its genetic basis having been largely refuted (5), this theory has now been supplanted by the “thrifty phenotype” hypothesis. The thrifty phenotype, originally applied to the susceptibility toward type 2 diabetes and later extended to obesity and its other complications, is thought to result from the complex interplay of environmental cues with the genome known as epigenetic mechanisms (6).

In this issue of *Diabetes*, Reinhardt et al. (7) report on testing their hypothesis that individuals who display greater reduction in energy expenditure during fasting or weaker increases during overfeeding (i.e., a thrifty phenotype) are resistant to weight loss. After an initial weight-maintenance period, the authors submitted 12 obese volunteers to 24-h fasting and overfeeding (200% of caloric expenditure), recording energy expenditure using room calorimetry as well as energy intake and fecal and urinary energy loss using combustion calorimetry. Participants then underwent a 6-week, inpatient, 50% caloric restriction diet. During the diet, their energy expenditure was monitored in a calorimetry room. Body composition was measured at baseline and every 2 weeks thereafter using DXA. Postcaloric-restriction body composition, energy expenditure, and urine and fecal energy loss on the weight-maintenance diet were

also all recorded. Physical activity was carefully documented using multiple band accelerometers, and a physical activity factor, based on the relative proportion of sedentary time, was derived to correct 24-h energy expenditure. Over the 42 days of caloric restriction, the measurement of caloric deficit compared to that calculated based on body composition changes differed, on average, by a mere 14 kcal/day, i.e., an error under 1% of the daily caloric balance. Using a rigorous trial design and meticulous assessment of caloric balance, Reinhardt et al. found that weak reductions of 24-h energy expenditure while fasting and sharp increases while overfeeding were each a predictor of further weight loss over the 6-week caloric restriction diet. Both associations were attributable to daytime rather than nighttime changes in energy expenditure, strongly suggesting that resting energy expenditure adaptation did not contribute to the observed association between the thrifty phenotype and the diet-induced weight loss.

The molecular mechanisms underlying this thrifty phenotype are currently unknown. Shifts in several mutually nonexclusive types of thermogenesis (or heat production) may be involved, including adaptive thermogenesis in response to environmental cues such as changes in temperature (cold-induced thermogenesis [CIT]), diet-induced thermogenesis (DIT), and nonexercise (or daily) activity thermogenesis (NEAT) (Fig. 1).

CIT can substantially increase energy expenditure, driven by the activation of brown adipose tissue and muscle shivering as well as nonshivering metabolism (8–10). Reinhardt et al. (7) controlled for environmental temperature, as adaptive thermogenesis to temperature would be expected to affect both nighttime as well as daytime energy expenditure.

DIT is the thermic effect of food, accounting for up to 10% of total energy expenditure. It has been proposed that stimulation of DIT partly drives weight loss after

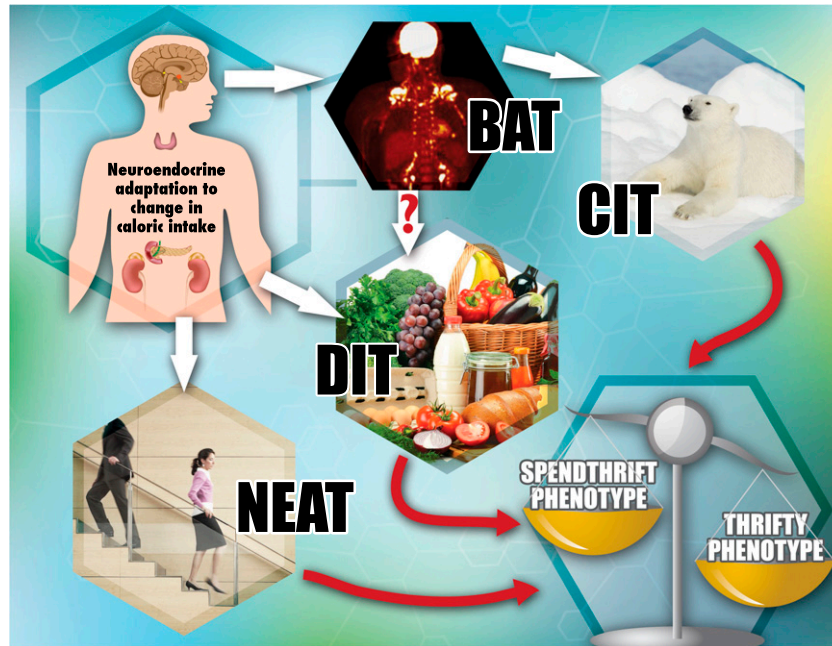


Figure 1—Possible mechanisms contributing to shifting the balance between “spendthrift” vs. “thrifty” phenotypes. Neuroendocrine adaptations to change in caloric intake modulate CIT, DIT, and NEAT. Brown adipose tissue (BAT) is an effector of CIT, but whether it may also contribute to DIT in humans is undetermined at the moment.

bariatric surgery (11). Shifts in DIT are caused by a variety of changes, including the rate of food intake and splanchnic circulation (12) and changes in dietary composition (13). Neuroendocrine adaptations such as changes in adrenergic tone and circulating adipokines (leptin, ghrelin, etc.) effected by modulation of brown adipose tissue metabolism (14) and/or changes in mitochondrial uncoupling in lean tissues (15) also cause DIT to shift. While dietary composition was carefully controlled for in the current study, the authors did not report on the levels of circulating adipokines or gastrointestinal hormones or on brown adipose tissue metabolism. The role of brown fat activation in DIT in humans remains controversial despite evidence from preclinical studies (16).

NEAT shifts also account for a significant proportion of total energy expenditure, especially in sedentary individuals (17). A drop in NEAT is observed in obesity. NEAT is also partly modulated by neuroendocrine signals during caloric imbalance, which may influence ensuing weight change. A rise in NEAT was shown to mitigate weight gain during overfeeding in some individuals (18). Reinhardt et al. (7) carefully monitored participant motion, using accelerometers on each of their four limbs and trunk. Activity-related energy expenditure was calculated using an index based on the fraction of sedentary time. Study participants were instructed not to partake in any high-intensity physical activity for the duration of the experiment. While the authors found that curbing the proportion of sedentary time was indeed related to weight loss, its effect was relatively weaker than that of the thrifty phenotype. It is nevertheless possible that a slight

increase in the intensity of daily activities resulting in higher NEAT may have been missed. This would have confounded the thrifty phenotype observed.

Thrifty phenotype-mediated modulation of weight loss was demonstrated by Reinhardt et al. (7) for diet-induced weight loss. Whether this phenotype also modulates weight loss in response to exercise or combined diet and exercise is currently unknown. Despite this limitation, the meticulous experimental work by these investigators offers a well-controlled demonstration that even small metabolic and/or daily activity adaptations to caloric imbalance matter when it comes to chronic energy homeostasis and weight loss. Obesity appears so insidiously slowly that it is almost a lifelong process for most individuals (19,20). Identifying adaptive mechanisms and how to tweak them to our advantage offer renewed hope in the fight against obesity and its complications. The carefully controlled study by Reinhardt et al. further supports the notion that sustaining small changes over time can eventually curb the global obesity pandemic.

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