How dieting makes some fatter: from a perspective of adipostat(s) and proteinstat(s) awaiting discovery

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Summary

'Dieting makes you fat' embodies the notion that dieting to control body weight predisposes the individual to acquire even more body fat. While this notion is controversial, its debate underscores the large gap that exists in our understanding of basic physiological laws that govern the regulation of human body composition. A striking example is the key role attributed to adipokines (e.g. leptin) as feedback signals between adipose tissue depletion and compensatory increases in food intake. Yet, the relative importance of fat depletion *per se* as a determinant of post-dieting hyperphagia is unknown. On the other hand, the question of whether the depletion of lean tissues can provide feedback signals on the hunger-appetite drive is rarely invoked, despite evidence that food intake during growth is dominated by the impetus for lean tissue deposition, amidst proposals for the existence of protein-static mechanisms for the regulation of growth and maintenance of lean body mass. In fact, a feedback loop between fat depletion and food intake cannot explain why human subjects recovering from starvation continue to overeat well after body fat has been restored to pre-starvation values, thereby contributing to 'fat overshooting'.

In addressing the plausibility and mechanistic basis by which dieting may predispose to increased fatness, this lecture integrates the results derived from the re-analysis of classic longitudinal studies of human starvation and refeeding. These suggest that feedback signals from the depletion of both fat mass (i.e. adipostats) and FFM (i.e. proteinstats) contribute to weight regain through the modulation of adaptive thermogenesis and energy intake, and that a faster rate of fat recovery relative to FFM recovery (i.e. preferential catch-up fat) is a central outcome of body composition autoregulation that drives fat overshooting. This confers biological plausibility for post-dieting fat overshooting - which through repeated dieting and weight cycling would increase the risks for trajectories from leanness to fatness. It also provides a system-physiology framework towards a more comprehensive molecular understanding of the sensor(s), signal(s) and effector(s) that constitute the adipostatic and proteinostatic control of body composition, with major implications for the management of obesity and cachexia.