Regulation of body fat content?

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A CLEVER AND INFORMATIVE PAPER by Lacy and Bartness (16) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology provides new data regarding the question of whether animals regulate their body content at a preferred level. Fifty years ago, Kennedy (15) proposed the existence of a “hypothalamic satiety mechanism” that served to prevent “an overall surplus of energy intake over expenditure, which would cause the deposition of fat in the depots.” A number of features comprised Kennedy’s original formulation. First was the assumption that “obesity results from excessive food intake.” Second, he posited that there was a ventromedial “hypothalamic centre . . . sensitive to the concentration of metabolites in circulation.” Third, this center inhibited eating as long as blood metabolite concentrations remained above a certain level. Accordingly, animals would become hyperphagic when their “hypothalamic centre” was damaged. Furthermore, energy-consuming processes stimulated food intake by diminishing blood metabolite levels, and a striking hyperphagia resulted in the face of extraordinary energy demands, as in lactation. Finally, body fat levels came into play because “the amount of fat in the depots could influence the level of blood metabolites.”

In the years following the publication of this seminal paper, a number of investigators embellished and transformed Kennedy’s ideas into what is now known as the “lipostatic hypothesis” of body weight1 regulation (e.g., Refs. 14, 21). Simply put, this kind of hypothesis posits the existence of a neural representation of an ideal body fat content (a lipostatic set point). Neuronal detectors are able to sense some blood-borne substance(s) whose levels covary with body fat content and compare this signal with the reference value. When the feedback signal deviates from the reference value, food intake and energy expenditure are adjusted accordingly until the signal is again aligned with the set point.

Note that this lipostatic hypothesis is substantially different from Kennedy’s original proposition. He did not suggest that body fat content was the regulated variable. Rather, he held that the medial-basal hypothalamic responded to blood metabolite concentrations and that “Such a mechanism need not discriminate between the causes of the variation in demand, nor exert any control over them, but would simply inhibit eating when the total demand was met.” Body fat content was seen as only one of many factors affecting blood metabolite concentrations.

How have these concepts fared over the years? The utility of the lipostatic set point concept has been the subject of much discussion. [See the exchange between Mrosovsky and Powley (21) and Davis and Wirtshafter (7) for a particularly thoughtful discussion.] Many have found lipostatic set points as a useful descriptor of the phenomenon whereby animals will return to a preferred body weight after experimental displacement in either direction (14, 21–23). However, even those who considered the concept of use in describing these weight changes conceded that the phenomenon did not require the existence of set point (21, 23).

It has been noted that even using the lipostatic set point as a descriptor is not without its hazards (13). Noting the tendency for animals to maintain a constant body weight in this way may give the appearance there is indeed a lipostatic set point and that this explains, rather than describes, the phenomenon. Such a facile explanation has the potential to set back progress in a field by years, because the problem is thought to have been solved (10). A more serious problem is that, for the uncritical, the existence of a lipostatic set point is inherently unfalsifiable, and scientific hypotheses are useful only to the extent that they can be falsified. If an experimental manipulation results in a transient change in body weight, it is taken as an example of returning to a lipostatic set point. On the other hand, if the experimental manipulation results in a new steady state for body weight, a true believer could argue that, rather than disconfirming the hypothesis, the manipulation has simply reset the set point.

The paper by Lacy and Bartness (16) in this issue is germane to both Kennedy’s original proposition and to the later lipostatic set point hypothesis. One of the strongest arguments in favor of the idea that total body fat content is regulated has come from experiments in which varying amounts of white adipose tissue have been extirpated surgically [see Mauer et al. (20) for review]. After lipectomy, animals of some, but not all species, return their body fat contents to presurgical levels within a few months. Species that exhibit seasonal cycles in body fat content are particularly adept at restoring their body fat levels and do so in a seasonally appropriate manner (6, 19). In general, presurgical body fat levels are restored by hyperphagia of other fat pads, rather than by regrowth of the excised depots (18, 20). Furthermore, animals typically do this without increasing their food intakes; instead, the extra calories that are stored come from savings in energy expenditure (20). Taken together, this work provides support for the idea that animals will defend some minimum level of body fat.

In a group of experiments that are obvious only in retrospect, Lacy and Bartness performed the complement to the lipectomy experiments using Siberian hamsters. In addition to removing...
body fat, they moved it within the body using autotransplants or added adipose tissue using transplants from other animals. Lipectomized animals accurately restored their body fat levels, but animals receiving autotransplants of epididymal fat pads or transplants from siblings did less well at compensating. These groups did not compensate for the transplanted fat pads, leaving them with more dissectible fat than controls or animals lipectomized and not given transplants. Thus the hamsters were able to compensate for lipid deficits, but not for surfeits. If body fat content is indeed regulated, then this regulation works better in one direction than the other.

This finding fits nicely with other work on regulation of energy balance. In many species, including human beings, any tendency to maintain a constant body fat content is easily overridden by the availability of palatable, calorie-laden foods. In a review of the literature of the role of leptin, Flier (9) proposed looking at these issues from an evolutionary perspective. Although originally conceived of as an adipostatic or antiobesity hormone (12, 24), leptin has been noteworthy in its ineffectiveness at preventing obesity. On the other hand, animals are highly responsive to deficits in leptin signaling, making adjustments in food intake, energy expenditure, reproduction, and other physiological processes (2). Throughout evolution and in much of the world today, humans and other animals have not been endangered by a surfeit of calories. Thus there would seem to have been little selective pressure to develop mechanisms to combat obesity. Indeed, antiobesity processes might even be counterproductive in most circumstances. On the other hand, obtaining enough calories for survival and reproduction has often been a challenge, and developing mechanisms for coping with energy deficits would be highly beneficial. Viewed from this perspective, the literature on both leptin action and on adipose tissue removal and transplantation makes a great deal of sense.

So how has the lipostatic hypothesis fared after all these years? Not too well, as it turns out. Kennedy proposed the existence of neural mechanisms to prevent obesity. Actually, the opposite seems to be true, and animals are far better at responding to underfeeding than overfeeding. Kennedy assumed that food intake was the primary determinant of body weight and fatness. At the very least, this notion is greatly oversimplified. Indeed, the literature is replete with examples of animals making enormous changes in body energy stores in the absence of changes in food intake (4, 5, 20). Kennedy assumed that a medial-basal hypothalamic “centre” was the crux of regulation of energy balance. Despite an inordinate current focus on the arcuate nucleus of the hypothalamus (e.g., Refs. 3, 8), we know now that the control of energy balance is very widely represented in the brain (e.g., Refs. 11), and it no longer makes sense to speak of centers.

Kennedy’s hypothesis and the thinking it begat continues to be enormously influential in guiding public opinion and also research into the physiology of energy balance. But after half a century, perhaps it is time to put the notions of centers, lipostats, set points, and the like behind us and move on. After all, “It’s OK to sleep with a hypothesis, but you should never become married to one” (17).

REFERENCES