White adipose tissue grafts—keeping in contact

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White adipose tissue is no longer viewed as a somewhat unglamorous organ but has instead emerged as one of the current “hot spots” in physiological and biomedical research. Two key developments underlie this change. One is the rapid rise in the incidence of obesity, which now affects nearly one-third of adult Americans (2) and more than one in five of adults in the United Kingdom (14). Obesity is, of course, defined by an expansion in adipose tissue mass and is associated both with a reduction in life expectancy (of ~8 yr) and by an increased incidence of several major diseases, particularly type 2 diabetes, coronary heart disease, and certain cancers.

The second major reason for the current focus on adipose tissue is the recognition that it is a major endocrine and secretory organ (4, 12, 16, 17). Indeed, even in an individual of normal weight, adipose tissue can represent the largest endocrine organ, accounting for approximately one-quarter of total tissue mass. The discovery of the cytokine-like hormone leptin in 1994 was the pivotal development in the recognition of white adipocytes as endocrine cells, the factor providing a key signal from the fat stores to the hypothalamus in the control of appetite and energy balance (19).

One of the classical approaches to investigating the control of energy balance and of adipose tissue mass has been the use of lipectomy—the surgical removal of the tissue. Lipectomy has been exploited periodically over several decades, and its particular attraction as an experimental tool lies in the fact that it allows the regulation of body fat to be examined directly (11). As such it provides an immediate approach to the question “Is body fat regulated?”. Other interventions aimed at altering fat content, such as manipulation of the quantity or nature of the diet, are, of course, indirect. The central observation from lipectomy studies is that the removal of adipose tissue from one site results in a compensatory increase in the mass of other adipose tissue depots. An important development of the lipectomy story is reported by Lacy and Bartness (8) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. Their report indicates that when partial lipectomy is undertaken in Siberian hamsters (Phodopus sungorus) and white adipose tissue is grafted back, an exaggerated response to the fat removal occurs in other depots when the graft is in physical contact with intact adipose tissue within the animal.

Lipectomy has been performed in a range of species (see 11), including rats, Siberian and Syrian hamsters (5, 9), ground squirrels (3), marsupials (fat-tailed dunnart; Smynthopsis cras-sicuadata) (6), and fat-tailed Kellakui lambs (11). It has also been performed on humans, although this has not been primarily for scientific purposes, but rather as liposuction aimed at the removal of fat from specific areas for essentially cosmetic reasons. The general picture is that removal of adipose tissue surgically from one depot leads to compensatory increases, over a period of weeks or months, in the size of other depots as though body fat itself is being “sensed” and regulated. Several of the species in which lipectomy has been performed, particularly hibernators such as the ground squirrel, exhibit major seasonal changes in adipose tissue mass, and in these cases the compensation is such that body fat is restored to the level appropriate to the point in the seasonal cycle.

Bartness and colleagues have progressively explored the effects of lipectomy in several recent studies using the Siberian hamster, which shows substantial seasonal (photoperiod induced) changes in adipose tissue mass and body weight. These animals compensate for the removal of adipose tissue by the customary increase in the size of other depots, at least in hamsters exposed to a long day length (10). Intriguingly, when epididymal adipose tissue was removed and then replaced in the subcutaneous region of the same animal (an autologous graft), there was compensation in the other depots—as if the animal had been subject to lipectomy, even though there had been no change in overall fat mass (7). Indeed, the animals actually overcompensated with an augmented increase in other sites. These changes were observed only with autologous grafts from the epididymal adipose tissue depot; there was no compensation from a nonautologous graft (epididymal fat from another animal) or if the inguinal fat was used (7). Overall, these observations indicate that total body fat per se is not being regulated in Siberian hamsters subjected to lipectomy with subsequent adipose tissue grafts.

In their current paper, Lacy and Bartness (8) have taken the issue further by examining the effects of the location in which adipose tissue grafts are placed. The dramatic finding is that physical contact between the autologous graft and native tissue results in greater responses in the other fat depots. The fat cell number was increased in native fat pads in contact with the grafted tissue, while distant fat pads that were not in contact exhibited an increase in fat cell size. These observations raise a number of questions, including the extent to which there is site specificity, both in terms of the source of the graft tissue (beyond epididymal and inguinal) and the range of possible locations for the graft. The mechanistic basis underlying such a response is, of course, of particular interest. Grafting presumably leads to revascularization of the transplanted tissue in time, but reinervation by sensory nerves does not appear to take place (8). There is, however, a compensatory decrease in sympathetic activity in distant adipose tissue depots of lipectomized animals (15).

The most likely explanation for these intriguing new results is that there is some form of paracrine interaction between the graft and the native adipose tissue with which it is in direct contact. This in turn, as speculated by Lacy and Bartness (8), might lead to changes in sympathetic activity in other fat depots via the sensory innervation of the pad adjacent to the

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graft. A reduction in sympathetic activity would not only result in reduced lipolysis but also increased adipocyte proliferation (1, 18). It would additionally be expected to lead to changes in the expression and secretion of those adipokines, such as leptin, which are under sympathetic control (13).

The identification of the putative paracrine or endocrine factor(s) that could initiate the events described here (8) is clearly an important challenge. One clue might be that since the grafted tissue does not contain an intact sympathetic innervation, then the (upregulated) factor might normally be subject to inhibition by the sympathetic system, as is the case with leptin (13). Overall, the fascinating observations reported in this issue may well lead to fresh perspectives both on the factors that influence total body fat and those that control adipocyte proliferation, with implications ultimately for obesity.

REFERENCES