First step to losing fat: central melanocortin signaling and sympathetic lipolytic drive

Hans-Rudi Berthoud

Neurobiology of Nutrition Laboratory, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana

THE DREAM OF MANY IS TO LIVE long and well, but the drastic increase in the prevalence of obesity worldwide (16) may quash these dreams. It is shocking to learn that one in three Americans born in the year 2000 will likely develop diabetes later in life and will lose up to 20 quality-adjusted life-years (17). Development of diabetes is strongly associated with increased adipose tissue mass, as a number of cytokines and hormones secreted from white adipose tissue can decrease insulin sensitivity (15). In turn, insulin resistance causes pancreatic β-cell hyperplasia and eventually collapse. Therefore, the metabolic syndrome could be delayed or prevented if adipose tissue mass could be reduced and there is strong interest in the development of lipolytic drugs. One of the signaling mechanisms to the adipocyte is through the sympathetic nervous system and the β-3 adrenergic receptor. Early clinical trials with selective β-3 adrenergic agonists are encouraging (1, 11, 22).

Storage of fat is an adaptive response to fluctuations in availability of food. Fat is stored when energy intake surpasses energy expenditure. This is demonstrated in hibernators, which increase fat stores substantially during summer and fall when food is plentiful and deplete fat stores during winter when little food is available. Similarly, many earlier human populations were often faced with periods of relative food abundance followed by famines. Those that were able to store more fat during periods of abundance were more likely to survive subsequent periods of famine. Thus there must have been significant evolutionary pressure for strong fat-storing mechanisms, and it would have been maladaptive to limit or tightly regulate the size of fat stores. However, in hibernators and in our human ancestors, fat stores rarely remained elevated for extended periods of time. Widespread obesity with constantly elevated fat stores is a recent phenomenon, and it is now clear that this condition has detrimental effects on other organs, leading to metabolic disease or syndrome-X, with diabetes, hypertension, cardiovascular disease, low-level inflammation, and early death (8, 15). Although it is not yet clear whether increased adipose tissue itself is the culprit causing metabolic disease or whether it is an innocent intermediary in the chain of events leading to it (9), reducing the size of fat depots should go a long way in eliminating the disease.

To enhance lipolytic mechanisms is thus one of the most rigorously pursued objectives of antiobesity therapy and of great interest to the pharmaceutical industry. The main physiological stimulus for lipolysis is lack of metabolizable fuels, when energy intake cannot match energy expenditure, particularly under conditions of strenuous exercise or cold. Because sensing fuels is as vital as sensing oxygen, this task is organized in a highly redundant manner. To protect brain metabolism, which is largely dependent on glucose, glucose sensors are located at strategic places in the brain and periphery. In the short-term, glucopenia and food deprivation produce a highly variable pattern of sympatho-adrenal system activity with increased sympathetic outflow to the adrenal gland, muscle, and sweat glands, but decreased sympathetic outflow to brown adipose tissue, heart, and skin blood vessels (5, 7, 14). This results in a concerted action to secure glucose supply through stimulation of hepatic glucose production and motor vigilance but avoid unnecessary energy expenditure.

In the longer-term, leptin secreted from adipose tissue itself is a powerful signal in the regulation of energy stores and food intake. Low leptin levels strongly stimulate food intake and protect energy mobilization from stores. When leptin increases above a certain level, it suppresses food intake and stimulates lipolysis. It has also long been known that the basomedial hypothalamus, a premier target of leptin action, plays a role in the mobilization of energy stores (2, 10, 20, 21), and there is considerable circumstantial evidence that melanocortin signaling at the melanocortin 4-receptor (MC4-R) is involved (12, 18, 19). However, details of these neural signaling pathways have not been clear.

In this issue of the American Journal of Physiology- Regulatory, Integrative and Comparative Physiology, Song and colleagues (20a), in a beautifully illustrated paper, provide new evidence for an important role of MC4-R signaling in the neural control of white adipose tissue function. Using pseudorabies transneuronal retrograde tracer in combination with in situ hybridization, they show that in the Siberian hamster, the majority of sympathetic premotor neurons projecting to the inguinal white fat depots express the MC4-R. Confirming their earlier work, the authors find the largest numbers of premotor neurons in classical autonomic areas of the caudal medulla oblongata and hypothalamus, and in many of these sympathetic outflow regions, over 70% of the retrogradely labeled neurons express the MC4-R. Although earlier functional studies suggested MC4-R signaling plays a role in lipolytic control, this study provides direct anatomical evidence for this signaling pathway. Pseudorabies virus injected into the fat pad is taken up by terminals of postganglionic sympathetic neurons and after retrograde transport to the cell bodies located in the prevertebral ganglia successively “jumps” to preganglionic neurons in the spinal cord and then to first-, second-, and higher-order premotor neurons in the brain. All neurons with multisynaptic projections to fat tissue can then be conveniently labeled by using an antibody that recognizes viral proteins. By choosing a series of time intervals between infection and histology, the author’s laboratory has previously provided insights into the hierarchy of first-, second-, and higher-order
premotor neurons projecting to white fat tissue (4). Among the areas harboring first-order premotor neurons are the caudal medullary raphé nuclei, the paraventricular nucleus, and the lateral areas of the hypothalamus. In all of these areas, a high percentage of fat-projecting neurons express MC4-Rs, and, conversely, a high percentage of MC4-R-bearing neurons project to fat tissue. However, there are much greater numbers of such double-labeled neurons in areas containing second- and higher-order premotor neurons such as the nuclei of the solitary tract and the adjacent reticular formation in the caudal medulla and most nuclei of the hypothalamus. These are all areas that receive dense melanocortin innervation (6, 23).

The observations by Song et al. (20a) strongly suggest that MC4-R-mediated melanocortin signaling within autonomic centers of the brain exerts powerful control over lipolytic processes in adipose tissue. It is also very likely that the findings hold up in rats and mice, as well as in humans. This is important to demonstrate, because as a hibernator, the Siberian hamster may need particularly strong central control over lipid storage and mobilization. The study provides plenty of new information for followup by functional studies. It defines many potential brain targets for microinjection of MC4R agonists and antagonists or for more permanent silencing or overstimulation of melanocortin signaling. Furthermore, although stimulation of lipolysis is the major function of sympathetic innervation to adipose tissue, it will also be interesting to look at the newly discovered endocrine functions of adipose tissue and their relationship to insulin sensitivity and inflammation.

Losing fat is the ultimate goal of obese subjects, and lipolysis is only the first step in an orchestrated process. Depending on the specific need, mobilized fat is directed to, and oxidized by, muscle, brown fat, and liver. The study by Song et al. (20a) has contributed significantly to our understanding of sympathethic nervous system control of white fat metabolism, but similar analyses need to be carried out for brown fat, liver, and the sympathetic nervous system control of muscle metabolism. Considering that muscle is by far the potentially largest fat burning organ, future research should be directed toward its control by the sympathetic nervous system.

**GRANTS**

This work was supported by National Institutes of Health grants DK-47348 and DK-071082.

**REFERENCES**