Brown Fat in Humans: Turning up the Heat on Obesity

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The looming pandemic of obesity and overweight, driven by ready access to high-calorie food and an increasingly sedentary way of life, poses a severe threat to global public health. The pathological accumulation of excess dysfunctional adipose tissue that characterizes obesity is a major risk factor for many other diseases, including type 2 diabetes, cardiovascular disease, hypertension, stroke, arthritis, and various types of cancer (1). A basic, but often misunderstood, concept is that weight gain is caused by a fundamental energy imbalance, when energy intake from food chronically exceeds energy expended by physical activity and metabolic processes (Fig. 1). Humans have evolved efficient biological mechanisms to acquire and defend their energy stores. A therapy for weight loss must, therefore, involve a decrease in food intake and/or an increase in energy expenditure.

In addition to the better-known white adipose tissue that specializes in lipid storage and undergoes pathological expansion during obesity, mammals are also equipped with thermogenic brown adipose tissue (BAT). BAT evolved in mammals to dissipate large amounts of chemical energy as heat. Brown fat cells possess large numbers of mitochondria that contain a unique protein called uncoupling protein 1 (UCP1). UCP1 functions to dissipate the proton motive force that is normally used to drive the synthesis of cellular ATP (2). As a consequence of UCP1 action, the energy in the mitochondrial electrochemical gradient is released in the form of heat. Indeed, BAT is a key thermogenic tissue in rodents and other small mammals, including newborn humans, that defends core body temperature in cold weather. The sensation of cold causes sympathetic nerves to release catecholamines in BAT that stimulate proliferation and heat production by brown fat cells (2). Studies in rodents have also unequivocally demonstrated that BAT plays an essential role in energy balance and that its activity profoundly influences body weight (3). Though BAT persists as a distinct tissue in small mammals, the major deposit of BAT in newborn humans (between the shoulder blades) regresses shortly after birth. Other depots of BAT have been known to exist in adult humans for many decades; however, estimates of its mass and activity had suggested that it would have a negligible impact on whole-body energy homeostasis (4,5). For these reasons, the role of BAT in adult human physiology and metabolism has not been carefully examined until now.

In this issue of *Diabetes*, the study by Saito et al. (6), together with three recent reports in the *New England Journal of Medicine* (7–9), unambiguously demonstrates that healthy adult humans have significant depots of metabolically active BAT. Positron emission tomography combined with computed tomography is commonly used to detect highly metabolically active cancer cells based on their uptake of large amounts of ^{18}fluoro-labeled 2-deoxyglucose (FDG). During such imaging studies, symmetrically localized depots of fatty tissue were frequently identified as hot spots for FDG uptake (rev. in 10). Though these tissues had all the attributes of BAT, formal proof has now been provided by Saito et al. and in the studies in the *New England Journal of Medicine*. Specifically, tissue biopsies corresponding to the positron emission tomography–positive regions have the morphological and molecular characteristics of BAT, including expression of the BAT-specific protein UCP1. Perhaps most importantly, and as expected of bona fide BAT, the tissue identified in adult humans is remarkably stimulated to take up glucose upon exposure to cold. In fact, Saito et al. show that BAT deposits are often or completely undetectable in people who are kept warm.

The central question that must now be addressed is whether BAT function significantly impacts energy balance and human obesity. Classic experiments in rodents have shown that BAT is activated and proliferates in response to overfeeding (11). This so-called "diet-induced adaptive thermogenesis" is an apparent compensatory mechanism to limit excess weight gain and obesity. Overfeeding studies in humans have provided evidence for dramatic interindividual differences in the energy cost of feeding (12–14). Both anecdotally and in controlled studies, it is known that individuals with similar dietary intake and exercise regimes exhibit dramatic differences in their tendency to gain weight. The extent to which BAT-mediated adaptive thermogenesis could account for some of this variability in metabolic efficiency is not known. The consensus from the recent human BAT studies, and especially the large-scale analysis by Cypess et al. (7), suggests an inverse correlation between BMI and BAT activity. Saito et al. also provide compelling data that BAT activity diminishes with age. This phenomenon would explain, at least to some degree, the tendency for people to gain weight during aging. Whether the age-related decline in BAT activity is caused by reduced sympathetic nerve function, reduced sensitivity of BAT to adrenergic signals, or cell-autonomous decreases in brown adipocyte differentiation or function is an open question for future experiments. Altogether, these new data strongly suggest that BAT, though often overlooked in human metabolism,

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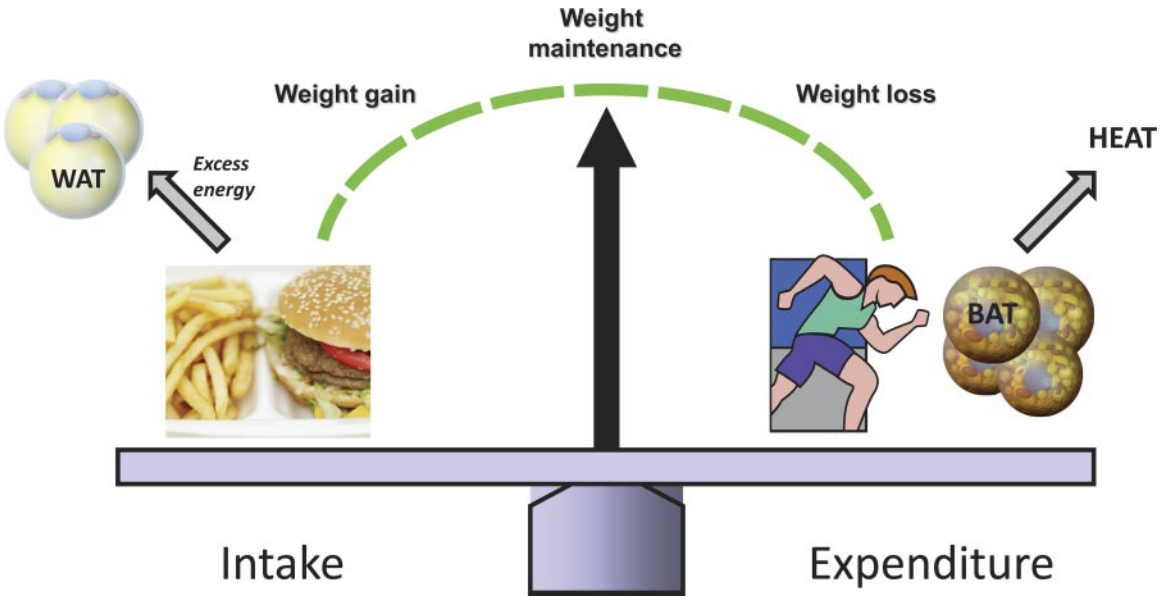

FIG. 1. BAT contributes to energy expenditure. Weight gain and obesity are caused by chronic periods of positive energy balance. Energy intake comes from food consumption, whereas the major contributors to expenditure are exercise and basic metabolic processes. The studies reviewed here suggest that BAT activity could impact daily energy expenditure. BAT dissipates energy as heat and can thus counteract weight gain. Interindividual variability in the amount or function of this tissue may impact body weight. In addition, therapeutic expansion/activation of this tissue may prove to be an effective therapy for obesity. WAT, white adipose tissue.

likely plays a significant role in the regulation of body weight.

Regardless of whether the BAT present in adult humans affects total daily energy expenditure, increasing the amount and/or function of this tissue could be a safe and effective therapy to limit obesity. The last several years have seen an explosion of information related to the transcriptional control of brown fat cell development, differentiation, and function. The Zn-finger transcriptional regulator PR domain containing 16 (PRDM16) has recently emerged as a dominant driver of brown fat cell fate (15,16). Bone morphogenetic protein 7 (BMP7) was also recently shown to specifically direct brown adipocyte differentiation, including induction of *Prdm16* and *Ucp1* gene expression (17). Synthetic chemicals or endogenous factors (e.g., BMP7 itself) that activate PRDM16 function or mimic its action in brown adipocyte development may be viable antiobesity drugs. Alternatively, it may be possible to engineer synthetic brown adipocytes ex vivo for autologous transplantation. Of course, it will first be important to establish that these developmental pathways are conserved in human BAT.

Although the idea of stimulating BAT activity to combat obesity is a rational approach, it is also conceivable that this would trigger counterregulatory mechanisms such as increased appetite to maintain energy homeostasis and preserve fuel reserves. Another potential concern is that activation of an expanded BAT compartment to levels that cause weight reduction may result in unacceptable heat generation and even socially unacceptable perspiration. The obesity field has already learned that target-based side effects can limit the utility of effective therapeutics; e.g., the anal leakage caused by inhibitors of lipid absorption from the gastrointestinal tract has prevented widespread use of these agents despite their efficacy for weight loss. Nevertheless, the new human data have invigorated interest and excitement in the function and physiological relevance of BAT. Hopefully, these findings can be translated into *1*) a better understanding of the mechanisms that work together to regulate body weight and *2*) novel therapeutic interventions to reduce the burden of obesity in our society.

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