Paul Trayhurn

Recruiting Brown Adipose Tissue in Human Obesity

Diabetes 2016;65:1158–1160 | DOI: 10.2337/dbi16-0002

COMMENTARY

Obesity remains a major biomedical challenge with its associated diseases, particularly insulin resistance and type 2 diabetes, imposing a substantial and increasing burden on health care systems. In the U.S., one-third of adults are classed as obese (BMI ≥30), while in the U.K., which has one of the highest incidence rates in Europe, 25% are obese. Conceptually, the treatment of obesity is simple: energy expenditure must exceed energy intake. In the late 1970s it was proposed, primarily on the basis of studies on rats and mice, that reduced expenditure on adaptive heat production (thermogenesis) associated with a specialized fat tissue—brown adipose tissue (BAT)—is central to the development of obesity. Correspondingly, for a period, stimulation of heat production in BAT was seen as a potential therapeutic route for reversing obesity, and there was a search for agents that would stimulate the activity of the tissue.

In the four centuries following its identification, different roles have been attributed to BAT, but in the early 1960s the tissue was firmly identified as a thermogenic organ generating heat through nonshivering mechanisms. Heat is produced by dissipation of the proton gradient across the mitochondrial inner membrane resulting in the uncoupling of oxidative phosphorylation (1). This process, which is critically dependent on the mitochondrial uncoupling protein 1 (UCP-1), is stimulated by noradrenaline from the sympathetic innervation acting through β_3-adrenoceptors (1). The concept that BAT is not only a thermoregulatory organ but also implicated in the regulation of energy balance with reduced thermogenesis (cold- and diet-induced) leading to obesity emerged through studies on obese mice and from overfeeding experiments on rats given a cafeteria diet (2). There was little progress, however, in the application of this concept to studies of obesity in humans, and interest in BAT waned. This was despite evidence in the 1980s for the presence of UCP-1 and a capacity for the activation of the tissue in adults (3).

A renaissance of interest in BAT was catalyzed in the late 2000s following the putative identification of multiple sites of the tissue in adult humans from investigations using fluorodeoxyglucose positron emission tomography (FDG-PET) (4). Use of FDG-PET and the detection of UCP-1 in the same areas resulted in the definitive identification of BAT in many adults (5,6). Further FDG-PET studies demonstrated that BAT activity is inversely related to BMI as activity was lower in obese subjects than in lean subjects and declined in older individuals (7–9). Insulin stimulates glucose uptake into BAT in humans, and acute cold exposure activates the tissue, as in rodents (6,10–12). Prolonged intermittent cold exposure, tantamount to cold acclimation, has been shown to lead to the recruitment of BAT in young, lean subjects (13–15) (Fig. 1). In contrast, only a limited increase in BAT metabolic activity was evident in patients with type 2 diabetes, these individuals being also overweight and older than those in other studies (16). It has therefore been unclear whether BAT is inducible in obese subjects, particularly those of older age, with a resultant enhancement of nonshivering thermogenesis. This is, of course, central to the proposition that BAT is a rational target for the treatment of obesity.

Whether BAT can be recruited in obese humans is directly addressed in an article by Hanssen et al. in this issue of *Diabetes* (17). The authors used FDG-PET to assess glucose uptake into presumptive BAT and white fat depots in a group of obese subjects before and after short-term "cold acclimation." Cold acclimation, amounting to exposure to 14–15°C for up to 6 h per day over 10 days, resulted in increased glucose uptake in BAT in 6 of the 10 subjects studied in which the tissue was evident. In one subject, BAT activity was also induced by cold acclimation where activity had been previously absent. As in other studies (7,8), BAT activity was inversely related to age both before and following cold acclimation. There was, however, no significant relationship between BAT activity and percent body fat (although an inverse trend was evident). In contrast to its effect on glucose uptake in BAT, cold acclimation did not increase glucose

Clore Laboratory, University of Buckingham, Buckingham, U.K.; Obesity Biology Unit, University of Liverpool, Liverpool, U.K.; College of Science, King Saud University, Riyadh, Saudi Arabia

Corresponding author: Paul Trayhurn, p.trayhurn@liverpool.ac.uk.

See accompanying article, p. 1179.

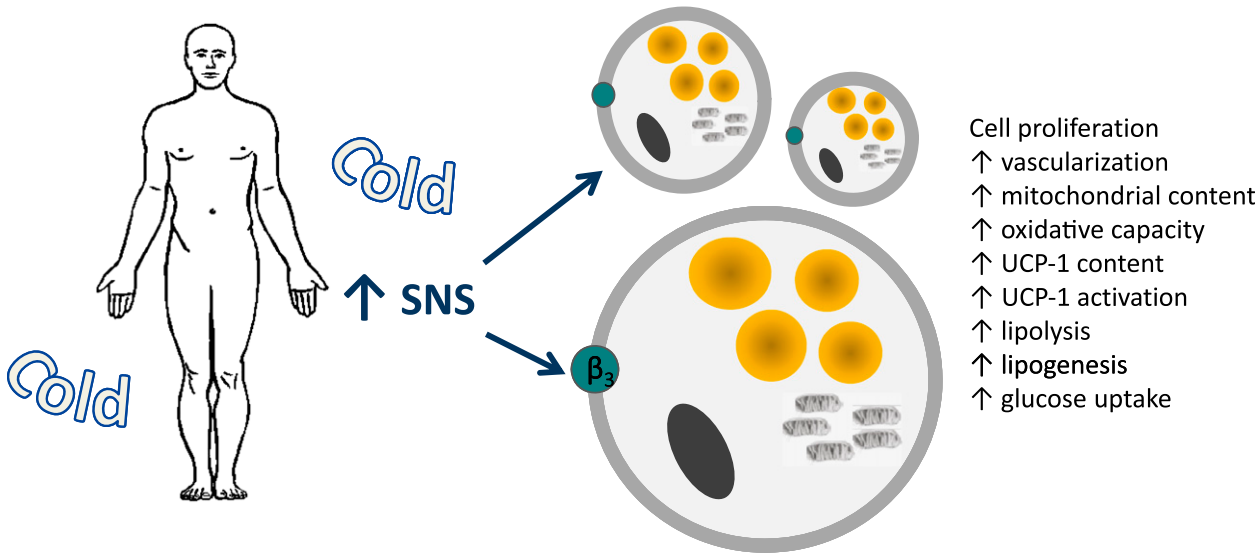

Figure 1—Schematic of the key effects of cold acclimation on the recruitment of BAT tissue. Cell proliferation is stimulated, and there are multiple changes within the brown adipocyte, particularly increases in the number of mitochondria and the concentration of UCP-1 in the mitochondria. Lipolysis, lipogenesis, and glucose uptake are stimulated as part of extensive changes in substrate utilization and cellular metabolism. SNS, sympathetic nervous system; β_3, β_3-adrenoceptor.

uptake into subcutaneous and visceral white fat depots, implying that "browning" had not occurred (or that brite/beige adipocytes are of limited physiological significance). In skeletal muscle, uptake was significantly increased in the triceps brachii but not in the scalene muscles, and increased translocation of GLUT4 to the sarcolemma was apparent.

Interestingly, the recruitment of BAT during cold acclimation was not associated with any elevation in total energy expenditure or in nonshivering thermogenesis. This may be a consequence of the modest increases in BAT observed, perhaps reflecting the limited acclimation stimulus that can be imposed on humans, or indicate that the tissue is only a minor contributor to expenditure in adults. The mean BMI of the subjects studied was 32.9 kg/m^2, with the highest being 36.8 kg/m^2; whether BAT can be recruited in severely obese subjects is an open question, particularly in the face of tissue hypoxia. Increased glucose uptake in BAT in obese subjects following prolonged cold exposure should affect glucose homeostasis (plasma glucose is reduced in the cold) and prevent induction of the obesity-associated insulin resistance. Indeed, mouse studies have indicated that brown fat is a major organ in glucose disposal and important in relation to insulin sensitivity; it has also been implicated in triglyceride clearance (18,19).

A key role for BAT in metabolic regulation, particularly during or following cold exposure, suggests that a lack of the tissue or reduction in its activity could have a role in the metabolic syndrome as well as in obesity (18,19). BAT has certainly reemerged as a therapeutic target in obesity, and the strategy of using selective β_3-adrenoceptor agonists has met with some recent success (20). Alternative approaches have also been considered, including potentiation of the induction of brite/beige adipocytes, BAT transplantation, and stem cell therapy. Whether the more technically innovative strategies are at all feasible remains unclear. There is also uncertainty as to whether the expansion and activation of BAT, or browning of white fat depots, could ensure a sustained and sufficient impact on energy balance and do so without raising cardiovascular concerns.

Duality of interest. No potential conflicts of interest relevant to this article were reported.

References

1. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev 2004;84:277–359
2. Himms-Hagen J. Brown adipose tissue thermogenesis and obesity. Prog Lipid Res 1989;28:67–115
3. Lean MEJ. Brown adipose tissue in humans. Proc Nutr Soc 1989;48:243–256
4. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab 2007;293:E444–E452
5. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509–1517
6. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. N Engl J Med 2009;360:1518–1525
7. Pfannenberg C, Werner MK, Ripkens S, et al. Impact of age on the relationships of brown adipose tissue with sex and adiposity in humans. Diabetes 2010;59:1789–1793
8. Yoneshiro T, Aita S, Matsushita M, et al. Age-related decrease in cold-activated brown adipose tissue and accumulation of body fat in healthy humans. Obesity (Silver Spring) 2011;19:1755–1760

9. Yoneshiro T, Aita S, Matsushita M, et al. Brown adipose tissue, whole-body energy expenditure, and thermogenesis in healthy adult men. Obesity (Silver Spring) 2011;19:13–16
10. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med 2009;360:1500–1508
11. Orava J, Nuutila P, Lidell ME, et al. Different metabolic responses of human brown adipose tissue to activation by cold and insulin. Cell Metab 2011;14:272–279
12. Ouellet V, Labbé SM, Blondin DP, et al. Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. J Clin Invest 2012;122:545–552
13. van der Lans AAJJ, Hoeks J, Brans B, et al. Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. J Clin Invest 2013;123:3395–3403
14. Lee P, Smith S, Linderman J, et al. Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. Diabetes 2014;63:3686–3698
15. Blondin DP, Labbé SM, Tingelstad HC, et al. Increased brown adipose tissue oxidative capacity in cold-acclimated humans. J Clin Endocrinol Metab 2014;99:E438–E446
16. Hanssen MJW, Hoeks J, Brans B, et al. Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus. Nat Med 2015;21:863–865
17. Hanssen MJW, van der Lans AAJJ, Brans B, et al. Short-term cold acclimation recruits brown adipose tissue in obese humans. Diabetes 2016;65:1179–1189
18. Bartelt A, Bruns OT, Reimer R, et al. Brown adipose tissue activity controls triglyceride clearance. Nat Med 2011;17:200–205
19. Stanford KI, Middelbeek RJW, Townsend KL, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. J Clin Invest 2013;123:215–223
20. Cypess AM, Weiner LS, Roberts-Toler C, et al. Activation of human brown adipose tissue by a β3-adrenergic receptor agonist. Cell Metab 2015;21:33–38