Commentary:

Recruiting brown adipose tissue in human obesity

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Word count – 985 text (excluding references)
Number of Figures and Tables – 1 Figure

Obesity remains a major biomedical challenge with the associated diseases, particularly insulin resistance and type 2 diabetes, imposing a substantial and increasing burden on healthcare systems. In the US, one-third of adults are classed as obese (BMI $\geq$30), while in the UK, 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 1970's it was proposed, primarily from studies on rats and mice, that reduced expenditure on adaptive heat production (thermogenesis) associated with a specialised 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 were attributed to BAT, but in the early 1960's the tissue was firmly identified as a thermogenic organ generating heat through non-shivering 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, critically dependent on the mitochondrial uncoupling protein 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 is 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 perspective to human obesity 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 catalysed in the late 2000's following the putative identification of multiple sites of the tissue in adult humans from investigations utilising fluorodeoxyglucose positron emission tomography (FDG-PET) (4). A combination 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, being lower in the obese than the lean and declining in older subjects (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). In contrast, only a limited increase in BAT metabolic activity was evident in patients with type 2 diabetes, these individuals also being overweight and older than those in other studies (16). It has

therefore been unclear whether BAT is inducible in the obese, particularly of an older age, with a resultant enhancement of non-shivering 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 has been directly addressed in a paper 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. BAT was also induced by cold-acclimation in a subject where activity was previously absent. As in other studies, BAT activity was inversely related to age, both before and following cold-acclimation. There was, however, no significant relationship with percent body fat (though an inverse trend was evident). In contrast to BAT, cold-acclimation did not increase glucose uptake into subcutaneous and visceral white fat depots implying that 'browning' had not occurred (or that brite/beige adipocytes are of limited physiological significance). With skeletal muscle, uptake was significantly increased in the triceps brachii, though not in the scalene muscle, 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, nor in non-shivering 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, the highest being 36.8, and whether BAT can be recruited in the severely obese is an open question, particularly in the face of tissue hypoxia. Increased glucose uptake in BAT in obese subjects following prolonged cold exposure should impact on 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, as well as being 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/reduction in its activity, could play a role in the metabolic syndrome as well as in obesity (18-19). BAT has certainly re-emerged as a therapeutic target in obesity, and the strategy of utilising 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 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.

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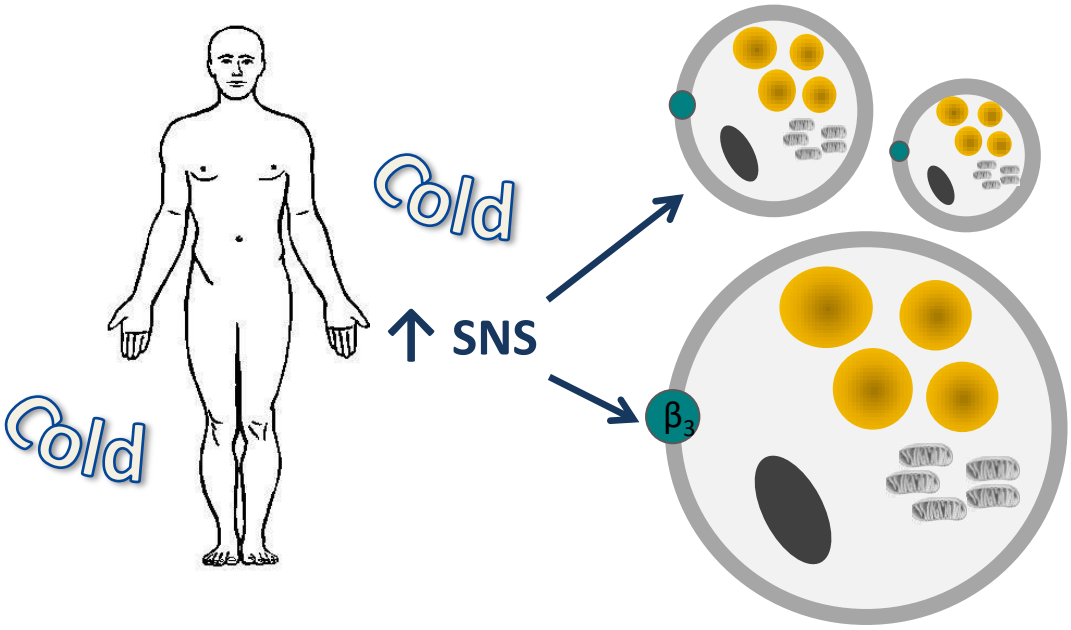
Legend to Figure

Figure 1 - Schematic of the key effects of cold-acclimation on the recruitment of brown adipose 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 UCP1 in the mitochondria. Lipolysis, lipogenesis and glucose uptake are stimulated as part of extensive changes in substrate utilisation and cellular metabolism. SNS, sympathetic nervous system; β_3, β_3-adrenoceptor.

Figure 1



Cell proliferation
↑ vascularisation
↑ mitochondrial content
↑ oxidative capacity
↑ UCP1 content
↑ UCP1 activation
↑ lipolysis
↑ lipogenesis
↑ glucose uptake