OBESITY

Slim without the gym — the magic of chilling out

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Cold exposure enhances brown adipose tissue activity, the beiging of white adipose tissue and might have antidiabetic and antiobesity effects. In new data, cold exposure induces and sustains brown adipose tissue in metabolically healthy individuals with obesity, suggesting that cold treatment might be clinically beneficial, even for those with increased BMI.

Refers to Hanssen, M. J. *et al.* Short-term cold acclimation recruits brown adipose tissue in obese humans. *Diabetes* http://dx.doi.org/10.2337/db15-1372 (2016)

As the obesity epidemic continues to lead to premature deaths from a broad range of pathological sequelae, including cardiovascular disease, type 2 diabetes mellitus and cancer, the urgency is greater than ever to identify approaches to promote weight loss, leading to healthier adipose tissue. This need is particularly pressing in light of the continued absence of a so called 'pharmacological magic bullet' that can lead to weight loss with minimal adverse effects. The concept that links activation of brown adipose tissue (BAT) or the enhanced browning/beiging of white adipose tissue (WAT) with a 'healthy' metabolic state is not new — investigators have been discussing the implications of changing the traditional ratio of WAT (energy storing) to BAT (energy burning) for the past decade[1]. BAT influences mitochondrial oxidation of free fatty acids and glucose in interscapular, perirenal, axillary, and paravertebral areas. Brite or beige adipose tissue, an intermediary between BAT and WAT, and widely characterized in the subcutaneous fat of rodents, can be induced in traditional areas of WAT by cold exposure, fibroblast growth factor 21, β-adrenergic agents, vascular endothelial growth factor, bone morphogenetic proteins, thiazolidinediones, natriuretic peptide and other factors[1]. Critically, the only known and effective non-pharmacological inducer of BAT is cold exposure. Evidence that BAT exists and is activated in humans after cold exposure comes from several important studies[2–4]. Since then, the extent of beiging of WAT and/or activation of BAT has been thought to be inversely correlated with multiple measures of obesity and potentially the metabolic syndrome[1]. However, only within the past few years has the recruitment of new BAT, enhanced activation of pre-existing BAT or induction of beiging in WAT become a clinically attractive concept to reverse symptoms of the metabolic syndrome. Despite vast preclinical interest in the process of browning of adipose tissue, the quantitative contributions of human BAT induction/activation towards energy expenditure are difficult to gauge. A new article published in *Diabetes* has shed some light on this question[5].

In earlier work, involving lean, healthy individuals, BAT recruitment could be driven by cold exposure, leading to improved glucose control and even a reduction in whole-body fat mass[6–9]. In the new study by Hanssen *et al.* the investigators tested whether short-term cold exposure can improve the metabolic state of humans with obesity, that is, those with an elevated BMI ($32.9\,kg/m^2 \pm 3.5$) in a prospective, single-arm clinical trial[5]. The team hoped that cold exposure would activate more pre-existing BAT and/or convert more WAT to a beige state. In particular they evaluated the quantitative changes in BAT activity, peripheral glucose uptake, and improvements in skeletal muscle function as a surrogate for favorable metabolic conditioning upon cold acclimation. The 10 participants, who were metabolically healthy with obesity, were exposed to 10 days of increasing periods of cold acclimation ranging from 2 to 6 h per day at 14–15°C, and analyzed both before and after treatment using ^{18}F-FDG-PET/CT imaging. The investigators detected both activated BAT and beige adipose tissue. With preconditioning thermoneutrality, these individuals were also subjected to muscle biopsies, which were repeated at the end of the cold exposure. Interestingly, 60% of the participants (incidentally corresponding to the youngest study participants; 19–39 years) demonstrated BAT activity before cold acclimation at baseline. All six of these individuals had greater BAT activity after cold exposure than before, as determined by increased PET imaging standardized uptake value (SUV) means from 2.3 ± 0.3 to 2.9 ± 0.3 ($P < 0.01$) and maximal SUV values from 8.8 ± 3.7 to 18.9 ± 5.5, ($P < 0.01$), but all ten individuals demonstrated some BAT activity after cold exposure as determined by glucose uptake using PET. Cold-induced ^{18}F-FDG uptake was unaltered in visceral or subcutaneous adipose tissue suggesting that, unlike in rodents, subcutaneous fat does not 'beige' in humans. However, this finding was still a meaningful measurement as baseline FDG uptake in these depots was proportional to cold-induced BAT activity. Average WAT ^{18}F-FDG at baseline was significantly higher in visceral than in subcutaneous adipose tissue. Activity of all fat depots was strongly associated with each other, with strong correlations between ^{18}F-FDG uptake in BAT and visceral WAT before and after cold acclimation, and between visceral and subcutaneous WAT after cold acclimation. Healthy subcutaneous adipose tissue, therefore, seems to predispose BAT to a more robust cold-induced response.

In contrast to subcutaneous and visceral adipose tissue, statistically significant glucose uptake in triceps brachii (SUV mean from 0.55 ± 0.10 to 0.59 ± 0.09; $P < 0.05$) and a trend towards increased uptake in the scalene muscle group after cold acclimation was observed (FIG. 1). Interestingly, muscle mitochondrial respiration in biopsy specimens was unaltered between pre-cold and post-cold acclimation. Total levels of GLUT-4 protein were also unaltered in pre-cold and post-cold acclimation muscle samples, but GLUT-4 recruitment to plasma membranes

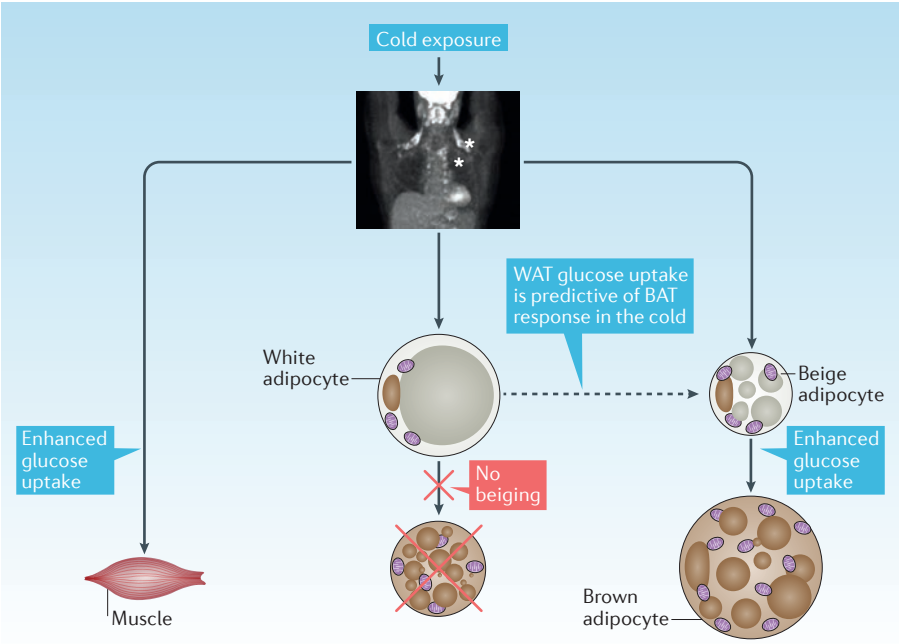

Figure 1 | **Cold-induced changes in BAT activity in healthy individuals with obesity.** WAT is unresponsive to cold based on glucose uptake measures; however, glucose uptake in WAT before cold-exposure is predictive of the BAT response to cold.

was greater after cold exposure, which partly explains the enhanced glucose uptake secondary to cold exposure. Plasma levels of hormones, fatty acids and glucose were unchanged by cold acclimation; the only other notable cold-induced change was increased proximal skin temperatures, although mean skin temperatures were unchanged.

Ultimately, BAT recruitment and activity were successfully increased in these metabolically healthy individuals with obesity who were exposed to the cold during the study. Importantly, these individuals were able to initiate browning of WAT in response to cold exposure to a similar extent as lean individuals.

Although individuals with obesity might have partially compromised WAT owing to increased fat storage, at a young age, the BAT of these people retained the ability to be activated by short-term cold exposure. Interestingly, in the results of a trial in human patients with type 2 diabetes mellitus, only a marginal increase in BAT activity after cold exposure was observed[10]. Consequently, identifying the events that lead to the loss of the effectiveness of short-term cold exposure over time is of great interest. Moreover, in the individuals studied by Hanssen and colleagues, no change in non-shivering thermogenesis was observed, despite the significant changes in BAT, at least not within the statistical limitations of a ten patient cohort study[5]. Furthermore, even though BAT was activated by the cold, no obvious beiging or browning of WAT depots seemed to occur, again suggesting the potential need for a stronger browning stimulus to affect WAT pads. In individuals with refractory WAT, browning might be more effectively achieved when combining cold exposure with a pharmacological agent, such as β3-adrenergic agonists. A large unmet need exists for such specific 'activating agents' to fully tap into the existing and emerging field of cold-induced BAT.

We learn from studies such as that completed by Hanssen *et al.* that the ability to take up glucose into several adipose tissue depots is strongly correlated between these regions. This finding is true even though BAT is the only fat depot that shows increased glucose uptake upon cold acclimation in humans. However, whether the ability of inducing BAT in humans has promise for sustained weight loss via increased energy expenditure, and/or whether the increased presence of activated BAT has a positive impact on general metabolic parameters and insulin sensitivity, is an outstanding question. This area of research is currently enjoying a high level of interest, which will hopefully lead to an improved understanding of the anti-obesity and antidiabetic contributions of the browning process.

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Competing interests statement
The authors declare no competing interests.