

## Brown adipose tissue affects lipid metabolism in humans

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Recent studies have shown the presence of functional brown adipose tissue (BAT) in adult humans in glucose and energy metabolism. This short study by Chondronikola *et al* published in *Cell Metabolism*<sup>1</sup> shows that during prolonged non-shivering cold exposure in obese/overweight individuals, brown adipose tissue is activated. This is associated with increased lipolysis, increased free fatty acid (FFA) oxidation and cycling. These changes in the BAT also affect insulin sensitivity in the white adipose tissue. This study provides insight into an unexplored role of function of BAT in lipid metabolism during prolonged cold exposure.

**Keywords:** human brown adipocytes, BAT, cold exposure, lipid metabolism.

### Introduction

Brown adipose tissue (BAT) is a unique organ found in mammals. Unlike white adipose tissue (WAT) which is mainly involved in storage of triglycerides as fat, the main function of BAT is heat production or thermogenesis. Uncoupling protein 1 (UCP1) is a mitochondrial proton channel which dissipates the mitochondrial proton gradient (that drives ATP synthesis) which is released as heat<sup>2</sup>. Fatty acids released from lipolysis of white adipose tissue bind and activate UCP1. Exposure to cold activates sympathetic nervous system which causes release of norepinephrine (NE) which binds to the G-protein coupled adrenergic receptors ( $\beta_3$ ,  $\alpha_1$ , and  $\alpha_2$ ) and triggers adipose tissue lipolysis<sup>2,3</sup>. Recent studies have shown that the adult brown adipose depots can be activated by cold exposure and  $\beta_3$  adrenergic-agonists<sup>2,4-67</sup>. The role of rodent BAT and its effect on lipid metabolism is well characterized. However, involvement of BAT in lipid mobilization and clearance in humans was still unanswered. This short study by Chondronikola *et al* determines whether there is a physiologically significant role of BAT on whole body lipid-metabolism in humans. Using metabolic tracers in conjunction with hyperinsulinemic-euglycemic clamps, they show that under mild, prolonged cold exposure, overweight/obese men show increased whole

body free fatty acid (FFA) turnover and oxidation, and adipose insulin sensitivity.

### Results

To stimulate BAT activation, 16 overweight/obese men (BMI  $30.3 \pm 2.1$ ) were subjected to prolonged non-shivering cold exposure (CE) ( $19.9^\circ\text{C} \pm 0.8^\circ\text{C}$ ) and thermoneutral conditions (TN) ( $26.2^\circ\text{C} \pm 1.2^\circ\text{C}$ ). Following CE, BAT showed significant increase in glucose uptake ( $[^{18}\text{F}\text{-FDG}]$  positron emission tomography scanning) and intracellular lipid use (measured by tissue radiodensity). Interestingly, liver or skeletal muscle (SKM) did not show any significant metabolic alterations. To assess the role of lipid kinetics, the authors infused stable isotopes and showed increased whole body lipolysis (expressed as rate of glycerol and FFA appearance) and FFA cycling, which suggested a potential role for BAT in lipid metabolism. These observed changes in lipid kinetics following CE were also reflected in increased concentration of plasma FFA and glycerol, which stayed elevated for 24 hours after CE. To assess the role of BAT in whole body insulin sensitivity, the authors infused U- $^{13}\text{C}$  palmitate in human subjects in conjunction with hyperinsulinemic-euglycemic clamp. Since lipolysis or fat breakdown counteracts insulin action, adipose insulin sensitivity was measured as insulin-mediated suppression of lipolysis. The authors

found that insulin sensitivity was associated with BAT volume. However, this correlation was abolished after adjusting for age and adiposity. Gene expression profiles in BAT in response to CE also showed induction of UCP1 and other fatty acid/lipid metabolism genes compared to TN conditions. However, CE did not induce any significant changes in subcutaneous adipose tissue. In accordance with previous rodent studies, a significant increase in BAT mitochondrial uncoupling was also observed following CE in human subjects.

### Conclusion

This short study by Chondronikola *et al* highlights the importance of BAT in systemic lipid metabolism. The authors show that BAT is activated following cold exposure in overweight adult humans and that it can affect whole body FFA turnover and insulin sensitivity. The role of BAT activation during cold has been very well characterized in rodents. This study is a follow-up on the previous report from the same group where they show the functional role of BAT in glucose homeostasis and insulin sensitivity in humans following cold exposure in lean adults<sup>8</sup>. The role of BAT in glucose disposal in adult humans is much debated. Previous reports have shown an inverse co-relation between central adiposity and BAT volume decreased BAT glucose uptake following cold exposure<sup>7</sup>. One of the drawbacks of this study is the assumption that increased BAT volume correlates with increased glucose uptake and insulin sensitivity since this does not hold true when adiposity is taken into account. Also, the authors fail to comment whether these obese/overweight subjects exhibit diabetes/metabolic syndrome owing to their high BMI. If these subjects are on insulin/insulin sensitizing drugs, it may have an effect on overall glucose disposal following cold exposure which may explain the discrepancy between BAT volume and adiposity. One surprising observation is the lack of [<sup>18</sup>F-FDG] uptake in skeletal muscle following cold exposure, since muscle is highly insulin sensitive and also contributes towards non-shivering thermogenesis. Given the increased BAT activity

and mass in women<sup>9</sup>, another important group to study would be lean and overweight women. Follow-up studies on the therapeutic effects on 'browning' on whole body lipid metabolism as a potential treatment for increasing energy expenditure in humans will be beneficial in combating obesity.

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