

## Adipose triglyceride lipolysis - adding fuel to the fire

Vidisha Raje, PhD

Department of Pharmacology, University of Virginia, 1340 Jefferson Park Avenue, Charlottesville, VA 22908, USA. Email: vbr9n@virginia.edu

**Abstract** Recent studies have shown the presence of functional brown adipose tissue (BAT) in adult humans and its role in thermogenesis. This study by Blondin *et al*<sup>1</sup> published in *Cell Metabolism* shows that similar to rodents; adult human brown adipose tissue uses lipids as its cellular fuel during thermogenesis. Inhibition of triglyceride lipolysis was associated with a shift in the skeletal muscle mediated shivering instead and a shift in fuel utilization from lipids to glucose. This study provides yet another confirmatory role of a functional brown fat in adult humans that is fueled by fatty acids.

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

### Introduction

Brown adipose tissue (BAT) and skeletal muscle (SKM) play an important role in body heat production, also known as thermogenesis. A cold stimulus triggers non-shivering thermogenesis (NST) in BAT whereas in the SKM, shivering is activated. Cold induced activation of the sympathetic nervous system (SNS) triggers catecholamine –induced adipose triglyceride lipolysis, downstream of the  $\beta$ -adrenergic receptors<sup>2</sup> and also stimulates glucose uptake in BAT<sup>3</sup>. In both brown and white adipose tissue, triglycerides are broken down into glycerol and free fatty acids (FFAs). In BAT, FFAs bind to and activate the uncoupling protein 1 (UCP1) in the inner mitochondrial membrane to fuel thermogenesis<sup>4</sup>. Relative to the contribution of circulating FFAs and glucose, the role of BAT intracellular fatty acids in thermogenesis is still unclear. Inhibition of lipolysis during chronic and acute cold exposure in rats decreased BAT oxidative metabolism suggesting a role for BAT intracellular stores of fatty acids in thermogenesis<sup>5</sup>.

The current study uses positron emission tomography (PET) with <sup>11</sup>C-acetate and <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>FDG) to measure the role of intracellular triglycerides and circulating

glucose on BAT oxidative metabolism during acute cold exposure in human subjects.

### Results

8 healthy men (BMI 24.5 kg/m<sup>2</sup>) were subjected to 180 minutes of cold exposure (18°C) with or without lipolysis inhibition, following a 150 minute baseline period at ambient temperature (22°C). Lipolysis was inhibited at the onset of cold exposure by ingestion of nicotinic acid. To calculate glucose, fatty acid and glycerol fluxes, stable isotopes ([3-<sup>3</sup>H] glucose, [U-<sup>13</sup>C] palmitate and [1,1,2,3,3-<sup>2</sup>H] glycerol) were infused at the onset of cold exposure. Nicotinic acid (NiAc) is a GPR109A agonist which inhibits the Gi coupled lipolysis downstream of SNS stimulation<sup>7</sup>. Treatment with NiAc suppressed cold induced activation of lipolysis (as assessed by rate of appearance of isotopic palmitate and glycerol), but interestingly increased overall carbohydrate oxidation in these subjects. The authors also noted an increase in BAT radiodensity which was abolished with lipolysis inhibition, suggesting activation of intracellular triglyceride lipolysis in BAT following cold exposure. Tissue specific oxidative metabolism was assessed by injection of <sup>11</sup>C-acetate. Cold exposure increased BAT oxidative metabolism and perfusion; however lipolysis inhibition showed an overall decrease in BAT oxidative metabolism. Using [<sup>18</sup>F]-FDG as a tracer, tissue specific glucose uptake and partitioning was calculated. One interesting observation the

authors made is that in the cold exposed subjects, lipolysis inhibition had a decrease in BAT total glucose uptake, but an increase in skeletal muscle glucose uptake. This co-related with an increase in shivering thermogenesis. NiAc treatment also increased the levels of circulating glucagon (induces hepatic glycogenolysis and gluconeogenesis) and cortisol (induces hepatic gluconeogenesis), both of which are known to increase the hepatic glucose output. This combined with increased skeletal muscle glucose uptake may explain why the NiAc treatment group showed an increase in glucose tracer appearance, but not total blood glucose levels during cold exposure.

### Conclusion

Endotherms, such as mammals, have a unique ability to maintain a stable core body temperature by virtue of heat production (thermogenesis) and heat dissipation. In mammals, the two major players in thermogenesis are: the skeletal muscle which is involved in contraction-dependent shivering thermogenesis and also futile calcium cycling dependent non-shivering thermogenesis (NST), and the brown adipose tissue which is mainly responsible for NST, mediated by uncoupled oxidative phosphorylation<sup>3,6</sup>. Uncoupling of oxidative phosphorylation is mediated by activation of the BAT mitochondrial uncoupling protein UCP1 by fatty acids.

Adipose tissue, skeletal muscle and liver are the major sites of insulin stimulated glucose disposal. In adipose tissue, glucose is stored as triglycerides, which can be made available to other tissues during periods of high metabolic demand such as cold stress. Norepinephrine released during cold stress induced sympathetic activation triggers lipolysis and also stimulates glucose uptake in BAT<sup>6</sup>. Previous studies from this group has shown a strong coupling between triglyceride lipolysis and glucose uptake during cold exposure in human subjects<sup>8,9</sup>. Obesity/insulin resistance is associated with an increased basal sympathetic activity, but decreased  $\beta$ -adrenergic responsiveness (reviewed in<sup>10</sup>). An interesting follow up study

would be testing the effect of NiAc during cold exposure in obese subjects. Alternatively, other adrenergic stress conditions where lipolysis is enhanced such as epinephrine infusion, physical trauma, surgery, burn injury or strenuous exercise will also provide a novel insight into effects of inhibition of lipolysis on glucose homeostasis. One of the major drawbacks of this study was the small sample size ( $n = 8$ ). However, this can be overcome as this study provides a direct comparison on the same individual on the effect of lipolysis inhibition when exposed to cold stress.

Cold stress induces white adipose tissue lipolysis and the released free fatty acids from circulation were considered to be the major fuel source during cold stress. The authors provide a novel role for intracellular BAT triglycerides for fueling non-shivering BAT thermogenesis independent of BAT blood flow in humans and highlight the metabolic fuel flexibility switching to shivering thermogenesis when fatty acids are unavailable. This study by Blondin *et al* supports the role of intracellular fatty acids mediated activation of BAT thermogenesis in humans by using metabolic tracers and lipolysis inhibitor Nicotinic acid (NiAc) and provides yet another evidence for the interplay between fat and glucose metabolism during conditions of acute stress.

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