Brown adipose tissue (BAT) stands out as the sole tissue able to substantially expend energy by leveraging uncoupling protein 1 (UCP1) to increase proton permeability through the inner mitochondrial membrane. The renewed interest in BAT in adult humans resulted from the growing use of 18F-fluoro-deoxyglucose (18FDG) PET coupled with either CT or MRI, and BAT continues to be defined and quantified in vivo according to features visualized through these imaging techniques (1). Inverse associations between the presence of 18FDG-positive adipose tissue and obesity, visceral fat, hyperglycemia, and diagnosis of type 2 diabetes (T2D) have been widely reported (2) and have led to the hypothesis that BAT metabolic dysfunction is a plausible contributor to obesity, T2D, and cardiometabolic diseases. Rodent studies have provided strong support for this hypothesis, as cold- and/or β-adrenergic agonist-stimulated BAT was shown to be a major driver of systemic clearance of glucose and circulating fat. Although BAT is unquestionably considered one of the hottest current targets for the treatment of obesity, T2D, and cardiometabolic complications, we posit that, in contrast to rodents, human BAT is not sufficient to combat cardiometabolic diseases. BAT glucose uptake does not reflect BAT thermogenesis. The first problem with the suggestion that BAT may play a role in cardiometabolic diseases involves BAT glucose uptake, which is used to define and quantify BAT's presence [...]
Brown adipose tissue (BAT) stands out as the sole tissue able to substantially expend energy by leveraging uncoupling protein 1 (UCP1) to increase proton permeability through the inner mitochondrial membrane. The renewed interest in BAT in adult humans resulted from the growing use of $^{18}$F-fluoro-deoxyglucose ($^{18}$FDG) PET coupled with either CT or MRI, and BAT continues to be defined and quantified in vivo according to features visualized through these imaging techniques (I). Inverse associations between the presence of $^{18}$FDG-positive adipose tissue and obesity, visceral fat, hyperglycemia, and diagnosis of type 2 diabetes (T2D) have been widely reported (2) and have led to the hypothesis that BAT metabolic dysfunction is a plausible contributor to obesity, T2D, and cardiometabolic diseases. Rodent studies have provided strong support for this hypothesis, as cold- and/or $\beta$-adrenergic agonist-stimulated BAT was shown to be a major driver of systemic clearance of glucose and circulating fat. Although BAT is unquestionably considered one of the hottest current targets for the treatment of obesity, T2D, and cardiometabolic complications, we posit that, in contrast to rodents, human BAT is not sufficient to combat cardiometabolic diseases.

**BAT glucose uptake does not reflect BAT thermogenesis**

The first problem with the suggestion that BAT may play a role in cardiometabolic diseases involves BAT glucose uptake, which is used to define and quantify BAT’s presence in almost all human studies. However, glucose uptake does not necessarily indicate BAT thermogenic activity. Most of the glucose taken up by BAT is metabolized to lactate and intracellular triglycerides (TG) (I, 3) and very little is used directly as a substrate for thermogenesis. Furthermore, insulin stimulates BAT glucose uptake without eliciting changes in tissue blood flow (4), suggesting that the physiological regulation of BAT glucose uptake and metabolism may act, in part, independent of thermogenesis. Cold-induced BAT glucose uptake is profoundly reduced in older, overweight men with or without T2D compared to lean healthy men, but without reduction in BAT thermogenesis as assessed by $^{13}$C-acetate PET (5). Further, a fructose-overfeeding regimen, capable of inducing visceral obesity, postprandial dyslipidemia, and systemic insulin resistance when prolonged for several weeks (6), selectively reduced cold-induced BAT glucose uptake without eliciting a change in BAT thermogenesis, measured by $^{13}$C-acetate PET after only two weeks of overfeeding (7). This reduction in BAT glucose uptake also occurred without any changes in circulating insulin, glucose, lipids, or change in the gut microbiota. Fasting-induced insulin resistance has also been associated with reduced BAT glucose uptake (8). Thus, reduced BAT glucose uptake is not necessarily indicative of reduced BAT thermogenesis, but may be a very early and sensitive indicator of nutritional and environmental exposures leading to dysmetabolism.

**Adults have small volumes of BAT**

The second problem with BAT as a major contributor to cardiometabolic disorders relates to its very low volume in humans compared with rodents. In humans, $^{18}$FDG-positive BAT volume typically ranges between 50 to 150 mL in most individuals acutely exposed to cold (9), and can increase an additional approximately 40% when rigorous cold acclimation is applied for 10 days to 4 weeks (10). Radiological mapping of adipose tissue depots containing $^{18}$FDG-positive BAT suggests upper ranges of 550 to 2550 mL, although only a small fraction of these volumes is demonstrably active metabolically (11). A hypothetical scenario in which individuals are exposed to a mild cold stimulus and have three different volumes of metabolically active BAT, 150 mL, 550 mL, or 2,550 mL, results in energy consumption rates of 12 kcal/24 hours, 46 kcal/24 hours, and 211 kcal/24 hours respectively, assuming sustained energy consumption and using BAT oxygen consumption rates derived from mild cold-exposure experiments involving $^{18}$O-$\text{O}_2$ PET (12). If calculated as a percentage of the increase in whole body energy expenditure stimulated from mild cold-exposure, which is approximately 1,440 kcal/24 hours, the values correspond to 0.8%, 3%, and 15% (5). Thus, for most individuals, current estimates of BAT thermogenic capacity are not compatible with a notable contribution of BAT to energy balance, even assuming continuous mild cold exposure, as performed in experimental settings. Likewise, BAT in humans contributes less than 1% to the clearance of systemic glucose, nonesterified fatty acids (NEFA), and plasma TG or dietary fatty acids from chylomicron TG, even under a nonrealistic degree of sustained cold exposure (I).
proton leak that suggests it as a target for the treatment of metabolic diseases. Indeed, none of these inter-tissue mediators, termed ‘batokines’, are specifically secreted by BAT or are directly demonstrated to be responsible for cold-induced metabolic improvements. The relative contribution of BAT versus WAT, skeletal muscles, liver, and/or immune cells to systemic levels of these ‘batokines’ is currently unknown in humans, but is likely to be small. Thus, while not formally excluded at this time, a role for BAT as an endocrine organ is not the most elegant explanation for the metabolic benefits of cold exposure.

BAT thermogenic characteristics are insufficient to treat obesity

BAT is an exciting tissue by virtue of its unique capacity to dissipate energy to produce heat as its principal metabolic product. However, our knowledge of human BAT pathophysiology is overtly reliant on BAT glucose uptake that is often uncoupled from BAT thermogenesis. The latter is almost never directly measured in vivo in human or even in animal investigations. Correlation is not causation, and the association between low ¹⁸F-FDG-positive BAT volumes and cardiometabolic diseases is likely driven by subtle changes in insulin sensitivity.

Figure 1. Cold-induced thermogenesis is a multi-organ process. BAT thermogenesis from uncoupling protein 1–mediated mitochondrial respiration likely contributes only a small fraction (i.e., less than 3%) of whole-body, cold-induced thermogenesis in humans. Skeletal muscle shivering and nonshivering thermogenesis drive most of the whole-body thermogenic response to cold. Glycerolipid and nonesterified fatty acid (GL/NEFA) substrate cycling activated in both WAT and BAT leads to systemic NEFA mobilization, likely driving NEFA reesterification in other organs (termed inter-organ GL/NEFA cycling) and also contributing to systemic energy expenditure.

Human thermogenesis is unlikely a BAT-dependent endocrine function

BAT-mediated mechanisms other than direct thermogenesis and energy substrate metabolism have been proposed. These include the secretion of biologically active metabolites or proteins that could act as endocrine factors to drive the metabolic benefits observed with BAT activation during cold or β-adrenergic stimulation (19). There is a priori no biological feature of BAT other than its unique capacity to produce heat through UCP1-dependent proton leak that suggests it as a target for the treatment of metabolic diseases. Indeed, none of these inter-tissue mediators, termed ‘batokines’, are specifically secreted by BAT or are directly demonstrated to be responsible for cold-induced metabolic improvements. The relative contribution of BAT versus WAT, skeletal muscles, liver, and/or immune cells to systemic levels of these ‘batokines’ is currently unknown in humans, but is likely to be small. Thus, while not formally excluded at this time, a role for BAT as an endocrine organ is not the most elegant explanation for the metabolic benefits of cold exposure.
and/or unmeasured dysmetabolic environmental exposures. Cold acclimation and/or β-adrenergic agonists can clearly activate and recruit BAT while simultaneously increasing energy expenditure and substrate utilization (10, 14, 15, 20). However, the small volume of BAT makes it unlikely to drive, by itself, the systemic metabolic benefits of cold exposure in humans. BAT never acts alone, as skeletal muscles, VAT, and probably other organs, contribute markedly to the changes in human metabolism observed under conditions where BAT is also metabolically activated (1). Coordinated activation of GL/NEFA substrate cycling, and likely other metabolic cycles from WAT, BAT, and other organs occurs and appears to play an important role in cold-induced thermogenesis. Indeed, in the absence of skeletal muscle shivering activity, there is no cold-induced improvement in peripheral insulin sensitivity (13). BAT thermogenic activity is the tip of a much larger multi-organ cold- and β-adrenergic agonist–stimulated response that needs to be better understood in humans before being exploited as a target for the treatment of cardiometabolic diseases.

Acknowledgments

ACC is the Canada Research Chair in Molecular Imaging of Diabetes. DPB is the Université de Sherbrooke/GlaxoSmithKline Research Chair in Diabetes. This work was supported by Canadian Institute of Health Research (CIHR) grants (MOP53094 and grant 299962). Many thanks to Anick Turgeon for contribution to the figure design.

Address correspondence to: André C. Carpentier, Division of Endocrinology, Faculty of Medicine, Université de Sherbrooke, 3001, 12th Ave North, Sherbrooke, Quebec, Canada J1H 5N4. Phone: 819.564.5243; Email: Andre.Carpentier@USherbrooke.ca.